Glycemic Index

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Contributor: Carneiro Lionel

Glycemic Index is an indicator originally used to help obese and diabetic people to manage their weight in glucose level by helping them choose adapted food. However, dietary interventions using low glycemic index food have shown encouraging improvements in people with brain diseases.

Keywords: Glycemic Index ; brain ; Health

1. Introduction

GI measures the impact of an individual food on the blood glucose level over time when compared to the effect of glucose itself (GI = 100). The glycemic response will thus depend on both the quantity and quality of carbohydrates (sugars, starch, or fibers) in the food. Consequently, a low-GI food (GI ≤ 55) contains high-quality carbohydrates and will not raise glycemia as much as a high-GI food (GI ≥ 70) for the same amount of carbohydrate. However, since the GI does not consider the amount of carbohydrate ingested, a glucose load (GL) value was developed.

2. Effect of a Glycemic Index Diet on Brain Function

Several studies have highlighted the role of a low-GI diet in insulin sensitivity, vascular system function, and weight management [21]. Recommendations in diabetic patients to help control their blood glucose level represent one of the most important applications of GI/GL indexes, despite some caveats in their interpretation. Besides this metabolic role, diets are used in neurodegenerative disorders, cancer, and even seizures. Such diet interventions started to gather interest following the discoveries of the influence of nutrients on brain function and notably on cognition, brain plasticity, and synaptic function, among others [9]. More recently, studies on the effects of specific diets on brain function gave rise to new evidence on the importance of nutrition in alterations and thus improvements. Low-GI diets have been used to ameliorate cognitive function, but also improve several pathological symptoms observed in specific neurological disorders, from dementia and depression, to ASD and AD (Table 2) [7].

Table 2. Example of various diets' composition for macronutrients with some examples of common foods associated with them. The low-GI diet highlighted in green is taken as a reference for a healthy diet.

	Low GL diet	Regular diet	Keto Diet	Modified Keto diet	MCT diet	Japanese diet	Mediterranean diet	Low GI diet	Western Diet	High GI diet	High GL diet
Carbohydrates	45%	45–55%	5–10%	15%	5–10%	45–55%	50–60%	15–20%	50%	45%	55%
Fat	35%	20–35%	70–75%	55%	30% MCTs 30% LCFA 10–15% others	20–35%	25–35%	60%	35%	35%	30%
Proteins	20%	10–35%	20–25%	30%	20–25%	10–35%	5–25%	20–25%	15%	30%	15%

Kcal	2200	2200	2200	2200	2200	~80% of regular	2200	2200	~120% of regular	2200	2200
Food	low GL foods	Fresh food, low processed food	Low carbs food, High Fat, fish, meat, eggs, vegetables, fruits, nuts, berries…	Keto diet with increased amount of carbs	Keto diet enriched in MCT rich food such as coconut oil	Fish, Fruits, seasonal food, green tea, soy, rice (brown)…	Olive oil, fruits, vegetables and legumes, low amount of meat and fish, moderate wine	Low GI foods enriched, high non digestible fibers…	Junk foods, processed food with added sugar, saturated fats, high GI food…	High GI food, low non digestible fibers	high GL foods

The low-GI diet highlighted in green is taken as a reference for a healthy diet.

Indeed, since glucose represents the main energy source for the brain, glucose level control appears critical for maintaining normal brain activity. Furthermore, neurological disorders are often associated with changes in neuronal activity, which can be targeted by modifying the availability of energetic substrates [22]. Nevertheless, diets can also be used in healthy people in a non-metabolic context. Indeed, different attempts to find out how to improve health through diet have been tested for decades in terms of physical activity, memory, and attention [23].

2.1. Effect of the Glycemic Index on Cognitive Function in Healthy People

Normal life requires a balanced diet with adapted macro- and micronutrients to maintain optimal cellular functions. Among other factors, cognition is likely to be altered by diet due to the high energy needs of the brain. Furthermore, the poor feeding habits of modern societies can very much alter normal cognitive function in healthy people. Therefore, a healthy diet can benefit healthy people and unhealthy populations. Aging, for instance, is often accompanied by cognitive decline. Therefore, determining the effects of dietary habits on cognition could be important for delaying aging-related declines. In this regard, the study of cognition in healthy elderly populations has tried to determine the role of GI/GL.

A recent study revealed that a low-GL diet contributes to maintaining a better cognitive function in the elderly. This result, along with others, support the role of GI/GL during the aging process (Table 3) [24–26]. Furthermore, these studies show either a decreased risk of dementia or AD occurrence. These observations confirm a negative effect of Western diets on cognition, which has been previously documented [27–29]. However, the study of Garber et al. indicates that only people with poor glucose regulation display a positive effect of GL [30]. High fat associated with high GI has been shown to induce insulin resistance, while the same fat content with a low GI improved insulin sensitivity [31]. Therefore, here, it is possible that the effects observed are due to insulin sensitivity improvement. Indeed, insulin is known to participate in cognitive function [32]. Furthermore, the improvement of glucose homeostasis could improve the energy supply to the brain and thus cognitive function.

Overall, the results presented do not completely address a role in healthy people since the effects observed are those on low glycemic control people. In support of that, previous analyses performed in younger populations over the past years have failed to give a precise answer on the effect of GI/GL on cognition in healthy people. In fact, a meta-analysis and study conducted by Philipou et al. revealed discrepancies in the results obtained on the role of GI/GL in cognition in healthy persons [33,34]. Such observations make it difficult to draw a conclusion on the relationship between GI/GL and cognition in healthy people (Table 3).

Younger populations of schoolchildren could also be targeted by diet adjustments to improve learning and memory functions. Indeed, different studies on adolescents have described a positive relationship between the GI/GL of breakfast meals and cognition through improving learning, but also attention, stress, and even mood [35–40]. Here, schoolchildren were divided into low- or high-GI breakfasts or no breakfast at all. Then, cognitive tasks were used to test the ability of the diets to inhibit cognitive interference (Stroop test [41]), memory tasks, focus, learning and mood, hunger and thirst, and fatigue in adolescents.

It was previously shown that adolescents who consume breakfast exhibit improved cognitive function compared to those who do not consume breakfast [42]. The higher glucose supply was then expected to help maintain the better performance displayed in the cognitive tests. This result confirms previous results discussed in the elderly. Nonetheless, introducing low- and high-GI breakfast groups to a breakfast omission group provides a more precise picture on the

putative mechanism involved. Thereby, both low- and high-GI breakfasts show improved adolescent cognition compared to the group without breakfast. Such a result supports the need of an energy supply for brain function. Moreover, low-GI breakfasts are more effective in these improvements than high GI breakfasts. This greater improvement related to low-GI breakfasts is also associated with lower glycemic and insulinemic responses. In fact, a high-GI breakfast group presented the lowest reaction time during the Stroop test. However, this increase in reaction was to the detriment of accuracy, which was significantly better in the low-GI group. Furthermore, this gain of accuracy was better maintained across the morning [38]. Finally, low-GI breakfast children display better results in cognitive tests assessing their working memory, as well as attention (Table 3).

All of these studies support the role of glucose in cognition improvement since both low- and high-GI breakfasts are beneficial compared to no breakfast. However, since a low-GI breakfast gives better results than a high-GI breakfast, the role of a high circulating glucose level in such an improvement is disputed [43]. Indeed, since a low-GI meal induces a lower increase in blood glucose compared to a high-GI meal, a high glucose level cannot be the main or only contributor [38]. In a previous study, a breakfast with low GI and high GL gave better results in terms of cognitive improvement than a low-GI/low-GL breakfast [37]. This result indicates that the energy intake is as important as the origin, which in this study, mainly came from carbohydrates. Therefore, high- or low-GL diets differ by the amount of carbohydrate. However, low-GI/low-GL and low-GI/high-GL diets contain the same amount of total energy (twice that of low-GL diets). Furthermore, high GL induces a more important increase in the glucose level than high GI. Interestingly, the cortisol level was higher in the high-GI group, suggesting that low GI could protect against the stress response (cognitive tests in the study). Finally, the authors also reported that adolescents fed the high-GL meal felt more confident, less sluggish, and less hungry or thirsty before the tests. The low-GI fed group, on the other hand, were happier, more alert and less nervous and thirsty before the tests. Previous research supports the findings of Micha et al., showing improved alertness and decreased fatigue following a low-GI/high-GL breakfast [44]. However, even so, cognitive test results are not affected by GL, since the observed effects were similar in all groups. This observation confirms the results mentioned above indicating that a high glucose level is not the main vehicle of cognition amelioration. Moreover, the glucose increase measured could suggest stimulation of the hypothalamic–pituitary–adrenal axis. In turn, this activation would result in the increased cortisol level measured. This loop would then serve as an anticipatory response to a stress [37]. Consequently, this decreased stress will contribute to the improved results obtained during the cognitive tests. Interestingly, a low blood glucose level after a fast alters the hypothalamic–pituitary–adrenal axis [45]. Low GI could then be responsible for lowering the cortisol level by inducing a lower blood glucose level. During a learning and memory task, this effect could represent an advantage for both memorizing and recalling (Table 3).

Table 3. Summary of human studies on diet effects on cognitive function in different neurological conditions.

Group	Diet	Method	Results	Limitation	Ref
Cognitive Healthy Elderly	No specific diet	Correlation between GI and cognitive score both assessed via questionnaire	Improved cognition in blood glucose regulation defect people	Different diets, background, food habits, medical history Questionnaire assessment of cognition only	[26–28,32]
Schoolchildren	Low GI breakfast vs High GI breakfast vs no breakfast Low GI/low GL vs low GI/high GL vs high GI/low GL vs high GI/high GL	Cognitive test for learning and memory, accuracy and speed score, stress, hunger and thirst assessment	Low GI improves cognition and accuracy and decrease stress	Schoolchildren tested only during the morning for the GI breakfast. No effect measured after lunch or on a long time period.	[37–43,46]

Adults	No specific diet	Correlation between the GI of the diet and cognitive score	No effect	Only study, group compared to elderly No adults group with high GI diet	[47]
Epilepsy	KD, modified KD, low GI	Pediatric patients, number of seizure	50% decrease in the number of seizure		[8,48]
Stroke	Vegetarian diets, Mediterranean diet High GI/GL diet	Stroke occurrence	Decreased risk of stroke with vegetarian diets Poor outcome following stroke with High GI/GL		[49–55]
Alzheimer's disease	High GI Diet, Low GI, healthy diet, KD, MCT diet, Mediterranean diet	Post mortem brain analysis, memory test	High GI associated with accumulation of Aβ Healthy diet decrease Aβ, improves memory and verbal communication	Observational studies, No interventional studies, no controlled diet, no longitudinal studies, no mechanistic studies, only hypothesis	[56–59]
Parkinson's disease	Japanese diet	PD rate	Low PD rate		[60,61]
Autism Spectrum Disorder	High GI or low GI diet	Animal studies, social behavior analysis	High GI increase ASD phenotype while low GI improve social behavior		[62–65]
Depression and Anxiety	High GI/GL	Rate of disease in a population	Increased depression and anxiety rate		[66]

According to studies in both adolescent and older populations, the glucose level and the source of carbohydrates are important in cognition, memory, and mood. However, healthy young populations display a strong effect, while the elderly only present a positive effect of a low-GI diet in groups with poor glucose regulation. It is possible that aging alters the sensitivity to GI/GL. Moreover, elderly studies have been conducted via questionnaires. This means that there could have been a large variety of meals, as well as nutritional habits, within the group studied. This could have influenced the results observed. Finally, it is worth noting that the elderly are cognitively healthy, but can display other medical histories and medications that could alter the real impact of diet on cognition. A longitudinal study should help determine how a specific dietary habit followed for a long time period will impact cognition in healthy populations. Additionally, the selection of healthy participants could help determine the effect on the development of age-related diseases, including cognitive deficits. To date, there is no study on the impact of a GI diet on cognition, mood, or memory in an adult population

exhibiting healthy conditions. Furthermore, the role of the glucose supply in brain activity is supported by the demonstration of blood glucose level variation, depending on a mental task and emotion in younger adults (≈25 years) [46]. More recently, younger adults (18–23 years old) and older adults (65 to 85 years old) were tested for memory recognition after a glucose or placebo injection. Only the older group showed an improvement in cognition. However, as previously mentioned, this population displays poor glucose control [67]. Overall, it is suggested that the glucose supply is still critical for maintaining a normal brain function, as shown by a decreased blood glucose level during high brain activity [46,68]. In addition, a higher cognitive decline in people with poor blood glucose control or insulin resistance was previously observed [47] (Table 3).

It is worth noting that Philippou et al. failed to draw a conclusion on the consensual effect of GI on cognition in their review [33]. Nevertheless, in regard of the key role of the blood glucose level in cognition, GI values can still be important. In fact, in previous studies, the task or parameter analyzed (recognition, learning, memory, mood, accuracy, etc.) and the population studied (different ages, ethnicities, and health conditions) could have affected the results, making comparisons difficult. Finally, the meal composition and time of the experiment (morning vs. noon vs. evening) are also important parameters that change between studies. Despite all of these issues, the review by Philippou et al. helps us make assumptions about possible mechanisms by which GI affects cognition. First, it is suggested that the blood glucose concentration, rather than the amount provided, influences memory enhancement. Therefore, since high GI induces a transient increase in blood glucose, while a low GI leads to a more sustained increase, although lower, a low GI is more likely to induce long-term effects [43,69,70]. In support of that, it has been described that the GI enhancement of cognition appears in the post prandial phase following a meal [43,69,70]. Another putative mechanism involves insulin that is affected by GI and plays a role in cognition. Indeed, insulin resistance alters this role in cognition regulation [71], while low GI improves the insulin sensitivity and should thus improve cognition [72]. Cortisol is another hormone involved in cognitive function modulation via the above-mentioned hypothalamic–pituitary–adrenal axis stimulation induced by a lower blood glucose level due to low-GI food [37]. Consequently, low GI is associated with a decrease in the stress response, triggering improved results in cognitive tasks (Table 3).

Altogether, it is difficult to conclude a clear effect of GI on cognition. Nevertheless, the schoolchildren studies gave the most solid results. Indeed, the results are interesting since GI and nutritional approaches could be important in childhood and during learning processes. Therefore, efforts need to be made to better understand the impact of nutrition on cognition. This knowledge would be useful for setting up new nutritional recommendations for children. Finally, the studies presented so far do not address in depth the mechanisms involved in cognition and the role of GI/GL. However, pathological studies have allowed the effects of diet on brain function to be tested with more attention.

3. Low-GI Diet and Neurological Dysfunctions

The previous studies are somewhat confusing and difficult to interpret, in addition to providing very little insight on the mechanisms involved. Interestingly, brain dysfunction research generates more information on the nutritional impact on brain function. Indeed, nutrition therapies used in brain dysfunctions have presented promising results in improvement of the pathology. Therefore, several reports on epilepsy, seizure, ASD, AD, and others have studied brain function after diet interventions. It should be noted that these studies have also permitted hypotheses on the mechanisms involved to be drawn. Therefore, such research could provide greater insights on the mechanisms in play in neurological diseases and metabolic regulation.

3.1. Epilepsy

Epilepsy has been associated with a ketogenic diet (KD) intervention for a long time [5]. KD is a low-carbohydrate and high-fat diet. Additionally, because of its side effects (ketoacidosis, hyperlipidemia, and hypoglycemia), other diets have been tested more recently (Table 2). Most of these diets are modified KDs with more carbohydrates, including a low-GI diet [73]. Overall, these diets have been shown to decrease the number of seizures in pediatric patients by at least 50% [74] (Table 3). Several attempts to elucidate the mechanisms in play have led to different hypotheses involving ketone bodies, mitochondria, or gene regulation. In these diets, the decrease in carbohydrates is compensated for by a higher amount of fat, which induces a shift in nutrient utilization in favor of lipid oxidation. This high rate of lipid oxidation in turn generates ketone bodies [8,75]. Ketogenesis usually occurs in the liver during fasting periods, but also in type 1 diabetes (due to a defect of glucose utilization because of the absence of insulin) or obesity. Neurological disorders have been associated with decreased glucose utilization. In this condition, the brain becomes dependent on ketone bodies for energy supply [12]. Ketone bodies are used as an alternative source of acetyl-coA, which is paralleled by a consumption of oxaloacetate. This stimulates the Krebs cycle and increases α-ketoglutarate. In turn, α-ketoglutarate forms high amounts of glutamate by consuming aspartate, whose level is then lowered. Finally, the glutamate produced is decarboxylated by the glutamic acid decarboxylase to produce the inhibitory neurotransmitter GABA (γ-aminobutyric acid) [76]. Interestingly,

GABA is described as an anti-seizure substance, and drug agonists targeting it are used in epilepsy [48,77–80]. Among these molecules, benzodiazepines enhance GABA's action [81]. In support of this mechanism, children treated with low-carbohydrate diets (low GI) present high levels of GABA in their cerebrospinal fluid [82].

Another hypothesized mechanism of ketone bodies is that they directly enter mitochondria and the tricarboxylic acid cycle (TCA) to be oxidized. In turn, the stimulated oxidative metabolism inhibits phosphofructokinase 1 and glycolysis. This direct metabolization of ketone bodies decreases the ATP produced in glycolysis that will open the ATP sensitive potassium channels (K-ATP) and decrease neuronal activity [83]. In support of that, a genetic model of drosophila exhibiting seizure-like activity upon mechanical stimulation showed a reduced number of seizures when given ketone bodies. Moreover, blocking the K_{ATP} channels or adding a GABA antagonist has been shown to partially reverse the effect of ketone bodies [84]. This partial effect suggests that other mechanisms are also involved. For instance, other studies indicate a blockade of vesicular glutamate transporter (VGLUT) transfer to the synapse by ketone bodies. Such a blockade will decrease the excitatory glutamate neurotransmitters and thus neuronal activity [85,86].

Mitochondria have also been linked to the anti-seizure effect of KD. Here, ketone bodies increase mitochondrial respiration and NADH oxidation, inhibit reactive oxygen species (ROS) production, and enhance ATP production [87]. All of these should prevent the mitochondrial permeability transition (mPT), which ultimately leads to cell death [88]. In support of that, mice with recurrent epileptic seizures show an increased threshold of mPT. This anti-mPT effect depends on cyclophilin D modulation (part of the mPT). Furthermore, learning and memory and long-term potentiation are decreased in these mice, suggesting a role in cognition [89]. However, this theory is contradictory to previous activity decreasing ATP production. Therefore, more research is needed to completely determine the role of ketone bodies in ATP production. Nevertheless, mitochondrial activity has been linked to neuronal function and diseases, while KD is known to improve mitochondrial activity [90]. Therefore, KD induces decreased mitochondrial ROS production compared to a normal chow, via changes in the gene expression of the oxidative pathway. Another possibility is that the increased NAD/NADH ratio induced by ketone bodies dampens ROS production [91]. Ketone bodies also improve the consumption of O2 within the respiratory chain. By doing so, KD decreases the rate of ROS production by the mitochondria. Since seizure is associated with oxidative stress, KD or modified KD could diminish the seizure occurrence in epileptic patients [92]. Moreover, besides having a direct effect on ROS production, KD also stimulates the antioxidant protein catalase, whose expression is stimulated by the activated peroxisome proliferator activated receptor γ2 (PPARγ2) transcription factor [92]. Here, PPAR activation occurs after histone hyper-acetylation following the inhibition of histone deacetylases (epigenetic regulation) [93,94]. In turn, PPAR upregulates antioxidant genes and downregulates pro-inflammatory genes (NFKappaB, cyclooxygenase 2, and iNOS) [95]. Histone deacetylase inhibitors are used as anti-inflammatory and anti-epileptogenic molecules [96]. Interestingly, ketone bodies are shown to inhibit histone deacetylase, although the precise mechanism still needs to be determined [97].

Finally, Rahman et al. hypothesized that ketone body neuroprotection could rely on the G-protein coupled receptor GPR109 recently identified, which is activated by ketone bodies and found in the brain. Moreover, mice fed a KD or infused with ketone bodies showed a decrease of ischemic infarcts dependent on GPR109. Furthermore, the authors demonstrated that the activation of GPR109 by ketone bodies occurs in infiltrated monocytes and macrophages. In turn, these cells produce prostaglandins and induce an anti-inflammatory response that reduces seizures [98,99]. Finally, the anti-inflammatory role of ketone bodies inhibits NLRP3 inflammasome assembly through the blockade of K+ efflux. However, the precise mechanism remains to be elucidated [100].

3.2. Stroke

Vegetarian diets (low GI and GL) have been described to lower the risk of stroke [101,102] (Table 3). Therefore, a relationship between GI/GL and stroke likely exists. On the other hand, a high-fructose diet that should have a high GI worsened post ischemic brain injury in rats [103]. In this study, the authors highlighted an important effect in the hippocampus with increased inflammation while neuronal plasticity was decreased, in parallel with neuronal loss. These changes lowered the neuronal performances during ischemic recovery compared to normal chow fed mice. These results support a role of the diet during the recovery period following a stroke. Here, the glucose level is also at play during the acute stage of a stroke and the recovery period. Therefore, diabetes is a risk factor for stroke [49,50]. The oxidative stress associated with hyperglycemia is expected to be the mechanism involved in the poor outcome following a stroke. This suggests that better glucose level control could help decrease the risk of stroke [104]. Diet intervention studies have provided interesting results in this regard. Therefore, a high-GL diet is associated with a poor outcome in patients with acute ischemic stroke [105]. Recently, Song et al. found that, in diabetic patients, this poor outcome does not depend on diabetes, but only on the diet's effect on glycemic variation. Furthermore, the authors suggested that chronic hyperglycemia is the main anticipated cause. Chronic hyperglycemia induced by a high-GL diet was previously shown to induce a poor outcome after a stroke [106,107]. One possible explanation for this is the cerebral hypo-perfusion or edema

associated with hyperglycemia, which leads to poor recovery from stroke [51,52]. Moreover, stroke is often linked to cytotoxicity, whose association with hyperglycemia dampens the recovery [53]. In addition, mitochondrial dysfunction due to lactate production from glucose metabolism has also been suggested. Here, lactate acidifies the intracellular environment and triggers mitochondrial dysfunction [108]. A rapid increase in blood glucose also leads to oxidative stress and endothelial dysfunction observed in diabetes [109]. Furthermore, high increases followed by periods of low levels are more deleterious than a continuous rise. Interestingly, high GI/GL increases glucose transiently, and thus has a negative effect on stroke outcome. Indeed, a dysfunctional endothelium has been described as a negative factor for acute ischemic stroke outcome [110]. Moreover, high-GI/GL diets induce insulin resistance [31] that will increase serum levels of fibrinogen and the von Willebrand factor (endothelial function), thus increasing the risk of stroke [111,112]. Therefore, high GI/GL should induce hypercoagulability and an increased risk of thrombosis. This phenotype is paralleled by an increase in small vessel diseases that could impair stroke outcome [113]. Finally, in a cohort of Chinese women followed for 10 years, a positive association between GI and the risk of stroke was observed, supporting the previous hypothesis [114]. Furthermore, the low-GI Mediterranean diet is associated with a reduction in the risk of stroke [115]. Finally, Lim et al. studied the role of diets in stroke recovery and cognition impairments. In their study, the authors described that glycemic variability with hyperglycemic episodes is detrimental to cognitive function recovery. Therefore, a diet avoiding amplitude oscillations for glycemia is more suitable for both vascular and cognitive function recovery after a stroke [116].

Overall, evidence indicates that high glucose increases induced by diet impact both the risk and outcome of stroke. The mechanisms in play are related to mitochondria and inflammation, as well as hypercoagulation. Moreover, chronic and rapid hyperglycemia following a meal is deleterious for both the risk and outcome. Therefore, a low-GI diet that induces a sustained elevation in blood glucose should be beneficial for recovery after a stroke, and decreases the risk of occurrence by improving cardiovascular function.

3.3. Alzheimer’s Disease (AD)

Diets are widely use in AD to help delay or slow the development of the disease [54,55]. Additionally, the relationship between AD and metabolic disorders (insulin resistance) means that this disease is considered as type III diabetes [117]. Therefore, nutritional approaches to studying AD have provided insights into the brain function in the pathology related to diet changes. Recently, it was reported that a high-GI diet increases the accumulation of amyloid β (Aβ) in brains of the elderly, which is a marker of AD, as well as a risk factor for the onset of the disease. In addition, these individuals showed a cognitive decline, and PET scan imaging demonstrated an increased association between Aβ accumulation and a high-GI diet [118] (Table 3). This interaction being independent of all other factors (age, sex, and education) indicates that high GI is highly involved in Aβ accumulation in aging populations and represents an increased risk factor for AD. In support of a key role of diet in AD onset, high-fat diet (HFD)-induced insulin resistance increases brain Aβ accumulation. However, mice deleted for IRS2 (insulin signaling) become insulin resistant, but do not accumulate Aβ, unless fed an HFD. Others have also shown that Aβ accumulation is accompanied by pTau aggregation (characteristic of AD) in an insulin-resistant AD mice model. Finally, oxidative stress and inflammation have been described in this mice model [119].

Overall, these results indicate that the Aβ burden is related to the diet, confirming that nutritional adjustments could help prevent AD onset and slow its progression [120]. In support of this, a recent review describes that a healthy diet can decrease the risk of AD by lowering oxidative stress and dampening Aβ accumulation [56]. Moreover, this review discusses the anti-inflammatory effect of a healthy diet. In AD, inflammation is caused by Aβ accumulation that stimulates the recruitment of microglia and astrocytes parallel to interferon gamma (IFNγ), interleukin 1β (IL1β), and tumor necrosis factor α (TNF α) secretion [57,121].

AD is characterized by a decreased glucose uptake and utilization by brain cells. However, the brains of AD individuals can still use ketone bodies [122,58]. Therefore, KD could be used in AD to slow progress of the disease or to delay the cognitive deficit. A medium-chain triglyceride diet (MCT diet) is a diet less restrictive in carbohydrates, but still ketogenic, and is used in AD [58]. The low content of carbohydrates forces the organism to use lipid oxidation as the energy source, which also produces ketone bodies. Therefore, such diets have a low impact on glycemia, making them low-GI diets. Brain energy metabolism and glucose uptake decreases are accompanied by mitochondrial dysfunction in AD [58]. Brain cells increased the utilization of ketone bodies during brain energetic deficiency, leading to a new “neuroketotherapeutic” strategy to compensate for the lack of glucose as an energy source [58]. Besides this energetic role, ketone bodies are also involved in neurotransmission and a reduction in oxidative stress and inflammation relevant to AD. Ketone bodies involve the mitochondria and their functional changes. As AD is associated with mitochondrial dysfunctions [123], ketone bodies could thus improve the disease phenotype. KD has also been shown to increase the number of mitochondria in the hippocampus, which could contribute to the improvement of AD [124]. Furthermore, since ketone bodies produce fewer ROS than glucose, they can participate in a decrease in the oxidative stress in AD [59,125]. This decrease in ROS production could be induced by stimulating the expression of uncoupling proteins (UCP), as shown previously [126,127].

Another possible mechanism is that reducing glutamate transport and improving GABA activity decreases the excitability of neurons and thus ROS production (see Section 3.1). In addition, KD was shown to upregulate antioxidant proteins (MnSOD, Glutathione, and Nrf2) [58]. Finally, KD inhibition of histone deacetylase can allow the expression of proteins improving cellular homeostasis and function (brain-derived neurotrophic factor (BDNF)), and in turn cognitive deficit in AD patients [128–132]. In support of the benefit of KD diets, mice models of AD also show decreased Aβ accumulation in the brain when fed a KD [58], while in humans, a medium-chain triglyceride (MCT) diet has been shown to result in an encouraging improved memory or at least the stabilization of cognitive function in AD individuals [58]. The direct effect of a KD in humans has been summarized by Taylor et al., who present an improvement of almost all the memory and verbal communication tests in AD patients under a KD [58] (Table 3).

Altogether, these results support an improvement of AD pathology by decreasing the carbohydrate supply and thus lowering the GI of the meals. The benefits depend on ketone bodies that help maintain neuronal activity, decrease oxidative stress, and stimulate gene regulation. However, a KD displays important side effects. Therefore, more research should be conducted to help better understand the mechanisms at play, and eventually develop a therapeutic approach targeting these mechanisms. Moreover, other low-GI diets could have similar beneficial effects to KDs, and thus must be tested. Overall, although there is solid evidence for ketone body involvement, the diets used in AD have several other effects that could be involved. Therefore, conducting more research to understand the role of low GI on the AD phenotype could help develop a diet adapted to the disease.

For instance, the Mediterranean diet (MD) is also protective against cognitive decline in AD [55]. MD is characterized by: a high intake of vegetables, legumes, fruits and cereals, and extra virgin oil (unsaturated fatty acids); low intake of saturated fats and meat; a moderate intake of fish; and a low to moderate intake of dairy products and wine during meals [133,134]. MD is low in carbohydrates, while high in fibers, and so can be classified as a low-GI diet (Table 2). MD is known to have numerous health benefits in cardiovascular or metabolic diseases, and also in cognition (lower decline) and in reducing the risk of dementia or AD [135,136]. Furthermore, people with mild cognitive impairment fed an MD show a decreased risk of AD onset, and improved memory, delayed recall, and global cognitive function [133]. Different studies suggest antioxidant, anti-inflammatory, or cognitive function enhancement, depending on the nutrient components. For instance, olive oil, as a main source of fats enriched in omega-3 and phenolic acid, is considered to be a main factor [133]. Olive oil decreases the glycemic response to a high-GI meal [137]. As such, olive oil helps lower the GI of a meal, and thus decreases the glycemic increase induced by a meal that could participate in the effects observed. In addition, since the carbohydrate content of MD is low or non-digestible, ketogenesis is expected and repeats the action described above. Accordingly, a modified Mediterranean–ketogenic diet has been described to be associated with changes in AD biomarkers in cerebro spinal fluid (CSF), suggesting that ketone bodies could be involved [138]. In addition, the observed changes in the brain could result from gut microbiota alterations, suggesting that nutrient digestion and/or absorption are important steps in AD onset and cognition. These results reinforce the relationship between nutrition, metabolism, and AD and cognitive function. Microbiota have been shown to interact with brain function through the metabolism of dietary fibers in certain bacteria that produce propionate or butyrate (short chain fatty acids (SCFA)). In turn, these SCFA exert brain effects via histone deacetylase, transcription factors, or antioxidant regulations. All of these effects will then provide neuroprotection and therefore protect against neurodegenerative disorders [139]. On the other hand, Western diets containing processed food and carbohydrates decrease the number of bacteria producing SCFA. By doing so, these diets have deleterious effects on brain and cognition. Interestingly, highly processed food will most likely have a high GI, while dietary fibers are low-GI carbohydrates, indicating that low-GI foods are protective against neurodegenerative diseases.

The gut–brain axis and nutrition have also been shown to participate in the pathophysiology of Autism Spectrum Disorder (ASD) [140]. Moreover, Parkinson's disease (PD) is improved by a KD. Altogether, nutrition and GI could have an impact on other neurological conditions.

3.4. Others: Dementia, Depression, Mental Health, etc.

Metabolism is often associated with pathological brain conditions. Therefore, the AD and PD risk increases with malnutrition and insulin resistance, while diet control is protective (138). Furthermore, insulin has been shown to increase dopamine transporter mRNA levels in the substantia nigra [141]. Therefore, it is assumed that a high-GI/GL diet could prevent PD by inducing high insulin secretion [142] (Table 3). However, the study suggesting a role for insulin is controversial, since high GI induces insulin resistance, while low GI improves insulin sensitivity [31]. Nonetheless, whilst the population studied presented a lower rate of PD while consuming high-GI food such as rice, it is likely that other dietary factors could be involved. Indeed, the Japanese diet is considered a healthy diet contributing to the expanded life expectancy observed in Japan. Therefore, cardiovascular-related death and neurodegenerative disease rates are amongst the lowest in the world [143]. The Japanese diet is characterized by raw ingredients used in meal preparation. The diet is low in fat and calories because most of the foods used are vegetables, fish, meat, and rice, providing an

excellent nutritional balance. This diet is low in red and processed meats, whole milk, refined grains, sweet drinks or alcohol, candy, and sweets, but enriched in fruits, vegetables, stevia sweeteners, and whole grains and fish products (Table 2). Overall, the Japanese diet is expected to be low GI (stevia has a GI/GL = 0) [142]. Therefore, the observed decrease in PD in the study of Murakami et al. could be due to an improved insulin sensitivity, rather than increased insulin levels. It was also described that a high-fat (high-GI) diet is responsible for a decreased number of dopaminergic neurons in the substantia nigra due to a reduced PPAR and inflammation. Therefore, a low-fat diet such as the Japanese diet could prevent these PPAR and dopaminergic neuron decreases and protect against PD [144]. The MD is also associated with a decreased risk of PD. Here, the microbiota changes induced by the diet are interesting since they are related to dietary fibers (lowering the GI) as a carbohydrate source in the diet. In addition, it strengthens the importance of the gut–brain axis in brain function and disease. Dietary fibers are known to stimulate the production of SCFA that could be part of the mechanism of protection against PD in the MD. Indeed, SCFA can improve insulin sensitivity, reduce inflammation, and stimulate brain-derived neurotrophic factor (BDNF) production, helping to protect against PD. Another possible mechanism occurs through the antioxidant-rich content of the MD. It should be noted that some of the antioxidant products in the diet can also stimulate SCFA production, reinforcing the role of these molecules in brain function and pathology [145]. In support of that, the SCFA concentration in the feces of PD patients is decreased compared to control individuals [146]. However, Shin et al. also observed an increase of plasma SCFA correlated with the PD severity [147]. This result suggests putative SCFA leakage from the intestinal lumen into the bloodstream. Nevertheless, further studies are needed to clearly address the impact of SCFA on PD, and more generally, the impact of diets.

Depression and anxiety are other brain diseases that exhibit a relationship with energy homeostasis [60,61]. Furthermore, depression has been studied in relation to GI/GL [148]. Although the results are inconsistent, it seems that high-GI/GL diets increase the risk of depression, as well as aggravate the score of the disease [148] (Table 3). Rodent studies showed that HFD impaired 5-HT neurotransmission, which increases anxiety behavior. The same group also reported decreased anxiety following Connexin 43 downregulation or phosphorylation, or treatment with metformin (activator of AMPK) [149–151]. In this context, metformin triggers a decrease in circulating branch chain amino acids (BCAA) that in turn contribute to the anxiolytic and antidepressant effect. BCAA have been previously linked to glutamate transport between intracellular to extracellular medium [152]. It was also observed that a metformin decrease of BCAA is due to the inhibition of ketone-derived BCAA production [153], suggesting that ketone bodies could be involved in depression and anxiety. Interestingly, in addition to ketones, anxiety and depression have been associated with oxidative stress, inflammation, and gut–brain communication [154,66]. Moreover, drugs have been developed to target glutamate signaling and its recycling in the synapse [155]. Therefore, it is likely that diet interventions could involve similar processes to those described above.

Autism Spectrum Disorder (ASD) is a neurological condition associated with behavioral and social interaction defects and that shows energy homeostasis dysregulation [156]. In fact, type 2 diabetes and obesity during pregnancy are risk factors for ASD in offspring [156,157]. Chronic inflammation observed in metabolic disorders and immune system activation that occurs during pregnancy appear to be key in the risk of ASD [158–160]. It is noteworthy that chronic inflammation can be decreased by a low-GI diet in obese subjects [161]. On the other hand, a high-GI diet increases advanced glycation end products (AGEs) that are involved in inflammation during obesity and diabetes. Indeed, the AGE activation of specific receptors results in C Reactive Protein (CRP) production and oxidative stress [162,163]. In support of this possible mechanism, Currais et al. demonstrated that mice offspring from high-GI-fed parents displayed increased brain inflammation, reduced neurogenesis, and characteristic ASD behaviors [164]. Dietary strategies have triggered improvement of the ASD phenotype after birth. For instance, KD given to a mice model of ASD improved the social behavior and decreased repetitive behaviors [165]. In another attempt, gluten-free foods decreased the inflammatory grade and improved the ASD phenotype. However, only some of the subjects showed improvement, while others failed to observe a benefit [166,167]. These studies, which used different diets, suggest that a specific nutrient or compound could be at play. Furthermore, inflammation is involved in the onset of the disease; however, other brain energetic alterations could also be present, but remain to be determined. Therefore, more research on both the understanding of ASD brain alterations and diet interventions to determine the role of specific nutrients or metabolic products needs to be conducted.

Microbiota are also associated with ASD behaviors [62,140,168]. Even if the role of gut microbiota is poorly understood, amino acid metabolism and inflammation are possible mechanisms participating in the phenotype observed. A low-GI diet induces changes in microbiota that are associated with ASD improvement. Therefore, the participation of a product with low-GI carbohydrates could be important. Finally, the ASD mice model shows decreased blood levels of methionine, also described in humans [63–65]. Interestingly, a high-GI diet also decreases the methionine levels [164]. Methionine is a precursor for DNA methylation and gene regulation [169]. In comparison, a low-GI diet maintains higher levels of methionine, suggesting that diet could improve ASD through epigenetic regulations. In line with the role of microbiota and low GI, sulforaphane, produced from low-GI vegetables (cauliflower and broccoli), has been identified as a putative

treatment in ASD. Indeed, sulforaphane given to autistic children improved their behavioral phenotype. Moreover, although the mechanism of action is not known, sulforaphane has been described to modulate oxidative stress, methylation, or apoptosis, and to be a potent neuroprotective molecule [170–174]. Overall, the identification of this molecule supports a beneficial role of a low-GI diet in ASD. It is noteworthy that, similar to other neurological conditions, ASD improvement through the diet is linked to oxidative stress, gene regulation, and inflammation. Moreover, a sulforaphane extract from vegetables is a promising molecule for the treatment of ASD. Further, other molecules produced or present in low-GI foods could also exist and participate in the beneficial effects, and would thus be useful in other neurological diseases (Table 3).

Intriguingly, oxidative stress, inflammation, ketone bodies, the gut–brain axis, microbiota, glutamate metabolism, and neurogenesis are all involved in the neurological conditions described. All of them can also be affected by the diet and especially the carbohydrate content and source. Therefore, low-GI diets are likely to improve neurological disorders, but may also be of interest in physiological conditions, since they help improve cognition and neuronal activity. A more generalized use of a low-GI/GL diet could help prevent or delay the onset of neurological disorders, while it could also help during the growing up period and in learning performances in childhood.

Although most of the mechanisms described appear to be common to the diseases described and are linked to diet intervention changes, no exact mechanisms and molecules involved in these beneficial effects have been precisely identified. Nevertheless, a lot of common pathways indicate a role of ketone bodies and SCFA. Therefore, more studies to determine diet involvement in the production of these molecules should be conducted to determine precise diet recommendations. Considering this, neurological disorders are likely to be successfully targeted by nutritional therapies.