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## Review

# *Mens sana in corpore sano*: Does the glycemic index have a role to play?

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**Abstract:** Although diet interventions are mostly related to metabolic disorders, nowadays they are used in wide variety of pathologies. From diabetes and obesity to cardiovascular diseases, through cancer or neurological disorders and stroke, nutritional recommendations applied to almost all diseases. Among those disorders, metabolic disturbances and brain function and/or diseases have recently been shown to be linked. Indeed, numerous neurological functions are often associated with perturbations of whole-body energy homeostasis. In this regard, specific diets are used in various neurological conditions such as epilepsy, stroke, or seizure recovery. In addition, Alzheimer's disease or Autism Spectrum Disorders are also considered as putatively improved by diet intervention. Glycemic index diets are a novel developed indicator expected to anticipate the changes in blood glucose induced by specific foods, and how they can affect various physiological function. Several results provide indications of efficiency of low glycemic index diets in weight management, insulin sensitivity, but also cognitive function, epilepsy treatment, stroke, or neurodegenerative diseases. Overall, studies involving glycemic index could provide new insight in the relationship between energy homeostasis regulation and brain function or related disorders. Therefore, in this review we will summarize main evidences on glycemic index involvement in brain mechanisms of energy homeostasis regulation.

Keywords: Cognition; nutrition; metabolism; neurodegeneration; ketone bodies; glycaemia; nutrition therapy

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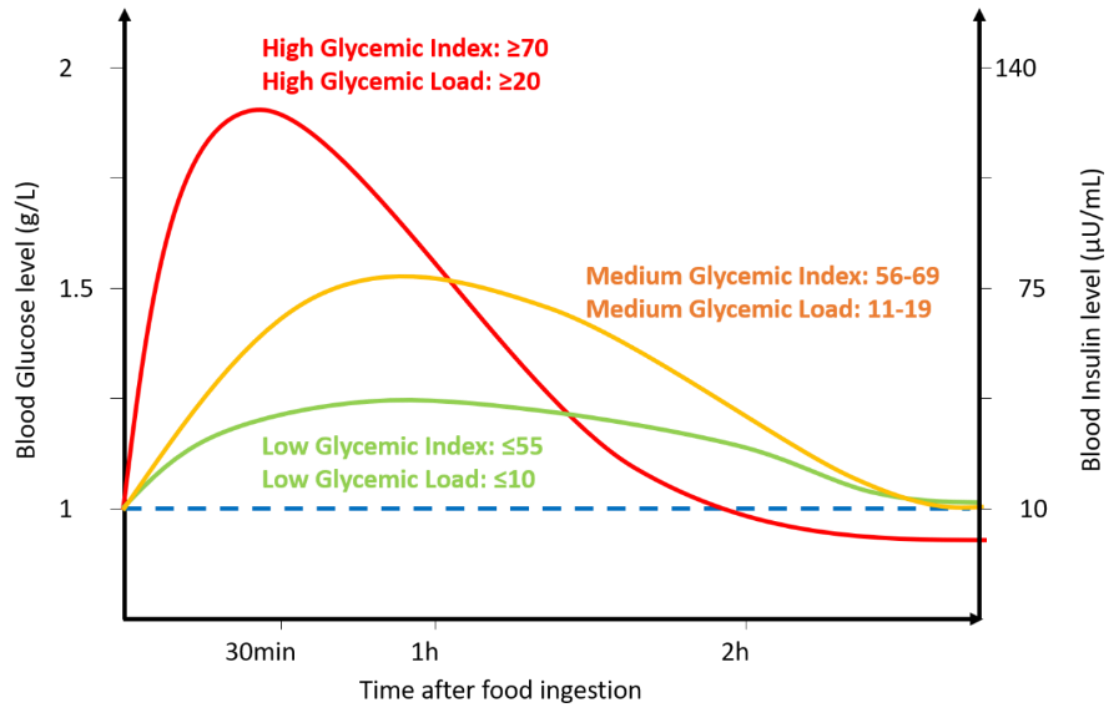
## 1. Introduction

Nutrition is part of the treatment for diabetes and obesity since decades. Thus, specific food choice to help control weight and glucose homeostasis is an important step in the establishment of a suitable diet. To assist patients, Jenkins et al. establish the glycemic index (GI) concept in 1981 [1]. GI measures the impact of an individual food on blood glucose level along time when compared to the effect of glucose itself (GI=100). The glycemic response will thus depend on both the quantity and the quality of carbohydrates (sugars, starch, or fibers) in the food. Consequently, a low GI food (GI ≤ 55), contains high quality carbohydrate and will not raise glycaemia as much as 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 has been developed. Thereby, GL represents a product of GI (quality of carbohydrate) and the quantity of carbohydrate ingested. Low GL is considered below 10, while high GL is above 20 when 10g of glucose has a GL of 10. (Table 1).

**Table 1.** Example of common foods with their corresponding serving size in g, GI carbohydrates per serving size in g and the resulting GL. Green indicate low, Orange indicates medium and Red indicates High GI or GL. [www.glycemicindex.com](http://www.glycemicindex.com),[1].

Food	Serving size (g)	GI	Carbohydrates per serving (g)	GL	Food	Serving size (g)	GI	Carbohydrates per serving (g)	GL	Food	Serving size (g)	GI	Carbohydrates per serving (g)	GL
Tuna	100	0	0	0	Fructose	10	23	10	2	Wheat	200	45	137	62
Salmon	100	0	0	0	Blackberry	60	25	4	2	Carrot Juice	250	45	24	11
Sardine	100	0	0	0	Grapefruit	120	25	11	3	Pineapple Juice	250	46	33	15
Makerel	100	0	0	0	Milk, full fat	250	27	12	3	Banana	120	47	24	11
Crab	85	0	0	0	American Cheese	28	27	2	<1	Lasagna	125	47	19	9
Eggs (chiken)	50	0	1	0	Cottage	28	27	6	2	Penne	125	47	94	44
Beef	100	0	0	0	Chickpeas, boiled	150	28	30	8	Butter	5	50	0	0
Chicken	140	0	6	0	Lentil	200	28	40	11	Mayonnaise	15	50	0	0
Goat	30	0	0	0	Beans, kidney	150	28	25	7	Mango	120	51	15	8
Pork	85	0	0	0	Garlic	3	30	1	<1	Tortilla	50	52	24	12
Lamb	85	0	1	0	Vanilla extract	4	30	3	0	Blueberry	150	53	18	7
Ham	85	0	0	0	Buttermilk	245	31	12	4	Kiwi fruit	150	53	16	9
Turkey	85	0	0	0	Lime	67	32	7	<1	Date	60	54	33	21
Duck	140	0	0	0	Broccoli	80	32	4	1	Orange Juice	250	55	26	14
Rabbit	85	0	0	0	Artichoke	150	32	14	4	Corn, Sweet	150	55	32	18
Macadamia	28	10	4	<1	Cauliflower	100	32	5	2	Cranberry Juice	250	55	33	18
Pecan	28	10	4	<1	Green Bean	55	32	4	1	Honey	25	55	20	11
Almond	28	10	6	<1	Asparagus	130	32	5	2	Brown Rice	150	55	33	18
Mushrooms	75	10	4	1	Radish	100	32	7	2	Ketchup	17	55	5	3
Cabbage	80	10	5	1	Mustard	5	32	1	<1	Apricots	120	57	9	5
Peanut Butter	55	14	5	6	Milk, skim	250	32	13	4	Potato	75	60	12	7
Peanut	28	14	6	1	Raspberries	150	32	8	3	Coca-Cola	250	60	26	16
Avocado	80	15	3	1	Ice cream	250	32	3	1	Fig (dried)	100	61	26	16
Zucchini	120	15	4	1	Pear	120	33	13	3	Beetroot	80	64	8	5
Cucumber	80	15	4	0	Apricot	120	34	9	3	Cantaloupe	120	65	6	4
Eggplant	100	15	6	2	Low Fat Milk	250	35	13	5	Sucrose	10	65	10	7
Tomato	100	15	4	1	Carrot	60	39	6	2	White rice	150	65	35	23
Celery	80	15	2	1	Plums	150	39	15	6	Couscous, boiled	150	65	35	23
Lettuce	100	15	3	1	Apple	120	40	16	6	Pineapple	120	66	10	6
Spinach	100	15	4	1	Orange	120	40	11	4	Sweet potato	130	70	17	12
Onion	10	15	1	<1	Strawberry	120	40	3	1	Crepe	30	71	7	5
Hazelnuts	28	15	5	<1	Pepper	2	40	1	<1	White bread	30	71	13	10
Red wine	150	15	4	<1	Apple Juice	250	40	30	12	Whole wheat bread	30	71	13	13
White wine	150	15	3	<1	Squash	80	41	30	8	Watermelon	120	72	6	4
Ginger	11	15	2	<1	Peach	120	42	11	5	Bagel	70	72	30	22
Yogurt, low fat	200	15	9	1	Beans, black-eyed	150	42	30	13	Goat milk	244	72	11	8
Soybean	190	16	56	9	Coconut	100	42	17	7	Rutabagas	385	72	33	24
Pistachios	28	18	8	1	Spaghetti	125	42	94	40	Popcorn	30	72	16	12
Walnut	28	20	4	1	Chocolate	28	43	16	7	Pumpkin	100	75	4	3
Cherries	100	20	16	5	Tagliatelle	125	44	90	40	Cornflakes	50	85	42	36
Lemon	60	20	5.5	1	Cranberry	110	45	8	1	Baguette	30	95	11	15
Pea	100	22	14	3	Endive	100	45	3	1	Glucose	10	100	10	10

In fact, low GI foods are digested and absorbed slowly compared to high GI foods. Therefore, low GI induce a limited increased in blood glucose that last for an extended period. On the opposite, High GI foods are easily digested and absorbed, and induce a rapid and high raise in blood glucose, followed by insulin secretion that often lead to a transient hypoglycemia (Figure 1) [2,3].



**Figure 1.** Schematic diagram of GI or GL influence on Blood glucose (left axis) or insulin (right axis). Low *vs* medium *vs* high GI or GL and their corresponding value range are indicated.

Diet interventions are used in physiological conditions such as sports for weight management and lose fat mass or gain lean mass. In addition, metabolic disorders are commonly associated with nutritional recommendations to induce weight loss, control glucose levels, or manage dyslipidemia [4]. Most notably, specific diets are also used in non-metabolic conditions since centuries. For instance, epilepsy treatment includes Ketogenic Diet (KD) since almost 100 years [5]. Interestingly, specific diets are used in cancer, cognitive improvement, neurological disorders, or mental diseases [6–9]. Most of the diets involved are characterized by low carbohydrate content or low GI food. Although GI/GL are determined for individual foods, diets based on these values have been developed, as well as methods of evaluation of GI/GL meals [10,11]. Therefore, the diets used in medical nutrition therapies are expected to be low GI diets. In fact, the impact of a meal on glycaemia is likely to be a key factor in disease development. Indeed, since glucose represents the main source of energy for our body in a healthy state, a disturbed glucose supply will alter normal function of the cells.

The brain represents 2% of the body weight while it is the main glucose consumer (20%) in humans [12]. Thus, brain control of glucose supply is finely regulated by the brain itself. Indeed, the brain possesses the ability to sense glucose levels and to trigger an adaptive response when glucose levels are low. Then, the brain will stimulate food intake or glucose production by peripheral organs. This will maintain a constant energy supply for brain activity [13]. Therefore, brain glucose detection is a key mechanism for both brain activity control and energy homeostasis regulation. Indeed, the brain plays a central role in the maintenance of energy homeostasis of the whole body. Moreover, nutrient sensing is one of the most regulated mechanism and involves specific regions such as the hypothalamus [14]. Among the nutrients sensed, glucose is the most studied and characterized [15]. Since, the GI impacts blood glucose level, meals composition based on GI are expected to involve the

brain circuits of glucose sensing. Moreover, low GI diets are also prone to increase ketone bodies production since they are low in carbohydrates [8]. Finally, carbohydrate composition of a meal induces changes in gut microbiota and in signals involved in food intake regulation and neurological disorders [16]. Overall, by involving key signals involved in both metabolic regulations and neuronal functions, GI diets could improve cellular and whole-body metabolism via brain regulation. Indeed, recent reports demonstrate a clear relationship between brain function and energy homeostasis. For instance, Alzheimer's disease (AD) shows metabolic defects including glucose uptake deficiency in the brain, insulin resistance, and even food intake alterations [17,18]. Furthermore, neurodegeneration is also associated with metabolic impairment and diabetes [19,20].

Although low GI diets have been developed to help diabetic people to manage their body weight and glycaemia, numerous effects in brain function have been described as well. Thus, cognitive function (memory, attention...) in healthy people, as well as improvements in brain function of patients with brain dysfunctions have been measured in relation to diets. Autism Spectrum Disorders (ASD), epilepsy, neurological disorders, or seizures have been all tested and display interesting results.

Thus, in this review, we aim to present the current understanding of diet and their GI/GL on brain functions, including cognition and energy homeostasis regulation. Further, the mechanisms involved will be described. Indeed, common mechanisms in both cognition and energy sensing could give new insight to develop novel therapeutic approaches in diseases associated to these functions. Finally, mechanisms involved should help understand the relationship between metabolism and neurological function. By so, novel nutritional approach for diseases treatment could be defined in addition to generate new nutritional recommendations for healthy people.

## **2. Effect of Glycemic Index diet on brain function**

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

**Table 2.** Example of various diets composition for macronutrients with some examples of common food associated. Low GI diet highlighted in green is here taken as references of healthy diet.

	Low GI diet	Regular diet	Keto Diet	Modified Keto diet	MCT diet	Japanese diet	Mediterranean diet	Low GI diet	Western Diet	High GI diet	High GI 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	20-35%	25-35%	60%	35%	35%	30%
					30% LCFA						
					10-15% others						
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 GI foods	Fresh food, low processed food	Low carbs food, High Fat, fish, meat, eggs, vegetables, fruits, nuts, berries...	Ket diet with increased amount of carbs	Keto diet enriched in MCT rich food such as coconut oil	Fish, Fruits, season 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 GI foods

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

### 2.1. Effect of 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 others, cognition is likely to be altered by the diet due to the high energy needs of the brain. Furthermore, poor feeding habits of modern societies could very much alter normal cognitive function in healthy people. Thus, healthy diet could benefit to healthy people as well as unhealthy populations. Aging for instance, is often accompanied with cognitive decline. Therefore, determining the effects of dietary habits on cognition could be important to delay aging related decline. In this regard the study of cognition in healthy elderly population has tried to determine the role of GI/GL.

A recent study reveals that a low GL diet contributes to maintain a better cognitive function in elderly. These result along with others support the role of GI/GL during aging process (Table 3) [24–26]. Further, these studies show either a decreased risk of dementia or AD occurrence. These observations confirm a negative effect of western diets on cognition that 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 is shown to induce insulin resistance while the same fat content with a low GI improves insulin sensitivity [31]. Thus, 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 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 on low glycemic control people. In support of that, previous analyses performed in younger populations in past years failed to give a precise answer on the effect of GI/GL on cognition in healthy people. In fact, a meta-analysis and study by Philipou et al. reveals discrepancies in results obtained on the role of GI/GL on cognition in healthy persons [33,34]. Such observations make it difficult to draw a conclusion on GI/GL and cognition relationship in healthy people (Table 3).

Younger populations of schoolchildren could also be targeted by diet adjustments to improve learning and memory functions especially. Indeed, different studies on adolescents describe a positive relationship between GI/GL of breakfast meals and cognition by improving learning but also attention, stress, and even mood [35–40]. Here, schoolchildren were divided in low or high GI breakfast or no breakfast at all. Then, cognitive tasks were assessed to test the ability 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 having a breakfast present improved cognitive function than others without breakfast [42]. The higher glucose supply was then expected to help maintain better performance in the cognitive tests. This result would confirm previous results discussed in elderly. Nonetheless, introducing low and high GI breakfast groups to a breakfast omission one provides a more precise picture on the putative mechanism involved. Thereby, both low and high GI breakfast show improved adolescents cognition compared to the group without breakfast. Such result support the need of energy supply for brain function. Further, low GI are more effective in these improvements than the high GI breakfast. This low GI higher improvement is also associated with a lower glycemic and insulinemic responses. In fact, high GI breakfast group presents the lowest reaction time during the Stroop test. However, this increase in reaction is to the detriment of accuracy that is significantly better in the low GI group. Furthermore, this gain of accuracy is better maintained across the morning [38]. Finally, low GI breakfast children display better results in cognitive tests assessing working memory as well as attention (Table 3).

In all, these studies support the role of glucose in cognition improvement since both low and high GI breakfasts are beneficial compared to a group without any breakfast at all. However, since a low GI gives better results than a high GI breakfast, the role of high circulating glucose level in such improvement is here disputed [43]. Indeed, since a low GI meal induces a lower increase in blood glucose compare 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 gives better results in cognitive improvement than a low GI/low GL breakfast [37]. This result indicates that the amount of energy intake is as important as the origin, which in this study comes from carbohydrates mainly. Thus, high or low GL diets differ by the amount of carbohydrate. However, low GI/low GL and low GI/high GL contain the same amount of total energy (twice than in low GL diets). Further, high GL induces a more important increase in glucose level than high GI. Interestingly, the cortisol level is higher in the high GI group, suggesting that the low GI could protect against stress response (cognitive tests in the study). Finally, the authors also report that adolescent fed the high GL meal feel themselves more confident, less sluggish, and less hungry or thirsty before the tests. The low GI fed group on the other hand, are happier and alert and less nervous and thirsty before the tests. Previous research support 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 are similar in all groups. This observation confirms the results above-mentioned indicating that the high glucose level is not the main vehicle of cognition amelioration. Moreover, glucose increase measured could suggest a stimulation of the hypothalamic-pituitary-adrenal axis. In turn, this activation would result in the increased cortisol level measured. This loop would then serves as an anticipatory response to a stress [37]. Consequently, this decreased stress will contribute to the improved results 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 cortisol lower level by inducing a lower blood glucose. During a learning and memory task, this effect could represent an advantage to both memorize and recall (Table 3).

Table 3: Summary of human studies on diet effect 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, 27, 28, 32
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	49
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, 38, 39, 40, 41, 42, 43, 46
Epilepsy	KD, modified KD, low GI	Pediatric patients, number of seizure	50% decrease in the number of seizure		8, 58
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		86, 87, 92, 93, 94, 104, 105
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 A $\beta$ Healthy diet decrease A $\beta$ , improve memory and verbal communication	Observational studies, No interventional studies, no controlled diet, no longitudinal studies, no mechanistic studies, only hypothesis	110, 111, 114, 117
Parkinson's disease	Japanese diet	PD rate	Low PD rate		141, 142
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		165, 166, 167, 168
Depression and Anxiety	High GI/GL	Rate of disease in a population	Increased depression and anxiety rate		150



According to studies in both adolescent and older populations, glucose level and the source of carbohydrates are important in cognition, memory and mood. However, healthy young populations display a strong effect while elderly present a positive effect of a low GI diet only on groups with poor glucose regulation. It is possible that ageing altered the sensitivity to GI/GL. Moreover, elderly studies were done via questionnaire. This meaning that it could have a large variety of meal as well as nutritional habits within the group studied. This could likely influence the results observed. Finally it is worth to note that elderly are cognitively healthy, but can display other medical history and medications that could alter the real impact of diet on cognition. A longitudinal study should help determine how a specific dietary habit will impact cognition in healthy population followed for a long time period. Also, the selection of a healthy participants could help determine the effect on the development of age related diseases including cognitive deficits. To date, there is no study in the adult population on the impact of GI diet on cognition, mood, or memory in healthy conditions. Furthermore, the role of 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 ( $\approx 25$  years) [46]. More recently, younger adults (18-23 years old) and older (65 to 85) were tested for memory recognition after glucose or a placebo injection. Only the older group shows an improvement in cognition. However, as previously, this population displays a poor glucose control [47]. Overall, it is suggested that glucose supply is still key for normal brain function as shown by a decreased blood glucose during high brain activity [46,48]. In addition it was previously observed a higher cognitive decline in people with poor blood glucose control or insulin resistance [49] (Table 3).

It is worth to note that Philippou et al. fail to conclude on a consensual effect of GI on cognition in their review [33]. Nevertheless, in regard of the key role of blood glucose level in cognition, GI values can still be important. In fact, in the previous studies, the task or the parameter analyzed (recognition, learning, memory, mood, accuracy...) and the population studied (different ages, ethnicity, health condition) could have affected the results, making difficult the comparisons. Finally, the meal composition as well as the time of the experiment (morning *vs* noon *vs* evening) is also an important parameter changing between studies. Despite all of these, the review from Philippou et al. helps assume possible mechanisms by which ones GI affect cognition. First, it is suggested that blood glucose concentration rather than the amount provided influences memory enhancement. Therefore, since high GI induces a transient increased in blood glucose while low GI leads to a more sustained increase although lower, the low GI is more likely to induce long term effects [43,50,51]. In support of that, it is described that the GI enhancement of cognition appears in the post prandial phase following a meal [43,50,51]. Another putative mechanism involves insulin that is affected by GI and play a role in cognition. Indeed, insulin resistance alter this role in cognition regulation [52], while low GI improve insulin sensitivity and thus should improve cognition [53]. Cortisol is another hormone involved in cognitive function modulation via the above mentioned hypothalamic-pituitary-adrenal axis stimulation by the lower blood glucose due to low GI food [37]. Consequently, low GI will be associated with a decrease in stress response, triggering the improved results in cognitive tasks (Table 3).

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

### 3. Low GI diet and neurological dysfunctions

The previous studies are somehow confusing and difficult to interpret in addition of providing very little insight on mechanisms involved. Interestingly, brain dysfunctions research brings more information on nutritional impact on brain function. Indeed, nutrition therapies used in brain dysfunctions gave promising results in improvement of the pathology. Thus, several reports in epilepsy, seizure, ASD, AD, and others studied brain function after diet interventions. To note, these studies also permit to draw hypothesis on the mechanisms involved. Therefore, such research could give more insight on the mechanisms in play in neurological diseases and metabolic regulations.

### 3.1. Epilepsy

Epilepsy is associated with ketogenic diet (KD) intervention since a long time [5]. KD is a low carbohydrate and high fat diet. Also, because of side effects (ketoacidosis, hyperlipidemia, and hypoglycemia) other diets have been tested more recently (Table 2). Most of these diets are modified KD with more carbohydrates including a low GI diet [54]. Overall, these diets are shown to decrease by at least 50% the number of seizures in pediatric patients [55] (Table 3). Several attempts to elucidate mechanisms in play led to different hypothesis involving ketone bodies, mitochondria, or gene regulation. In these diets the decrease in carbohydrates is compensated by 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 [8,56]. Ketogenesis usually occurs in the liver during fasting periods, but also in Type 1 diabetes (due to 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 will be used as an alternative source of acetyl-coA which is paralleled by a consumption of oxaloacetate. This stimulates the Krebs cycle and increases  $\alpha$ -ketoglutarate. In turn,  $\alpha$ -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 ( $\gamma$ -aminobutyric acid) [57]. Interestingly, GABA is described as anti-seizure, and drugs agonists targeting it are used in epilepsy [58–62]. Among these molecules, benzodiazepines enhance GABA action [63]. In support of this mechanism, children treated with low carbohydrate diets (low GI) present high levels of GABA in their CSF [64].

Another hypothesized mechanism of ketone bodies is by entering directly in mitochondria and the tricarboxylic acid cycle (TCA) to be oxidized. In turn, the stimulated oxidative metabolism inhibits the 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 [65]. In support of that, a genetic model of drosophila exhibiting seizure-like activity upon mechanical stimulation shows reduced seizure when given ketone bodies. Moreover, blocking the K-ATP channels or adding a GABA antagonist partially reverses the effect of ketone bodies [66]. This partial effect suggesting other mechanisms in play as well. For instance, other studies indicate a blockade of Vesicular glutamate transporters (VGLUT) transfer to the synapse by ketone bodies. Such blockade will decrease the excitatory glutamate neurotransmitters and thus neuronal activity [67,68].

Mitochondria has also been linked to the anti-seizure effect of KD. Here, ketone bodies increase mitochondrial respiration, NADH oxidation, inhibits reactive oxygen species (ROS) production, and enhance ATP production [69]. All of these should prevent mitochondrial permeability transition (mPT), which ultimately leads to cell death [70]. In support of that, mice with recurrent epileptic seizures show an increased threshold of mPT. This anti-mPT depends on cyclophilin D modulation (part of the mPT). Further, learning and memory and long-term potentiation is decreased in this mice, suggesting a role in cognition [71]. However, this theory is in contradiction with a previous activity decreasing ATP production. Therefore, more research is needed to completely determine the role of ketone bodies on ATP production. Nevertheless, mitochondria activity has been linked to neuronal function and diseases, while KD is known to improve mitochondrial activity [72]. Thus, KD induces

a decreased mitochondrial ROS production compared to a normal chow, via changes in gene expression of the oxidative pathway. Another possibility is through the increase NAD/NADH ratio by ketone bodies that will dampen ROS production [73]. Ketone bodies also improve the consumption of O<sub>2</sub> within the respiratory chain. By 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 [74]. Moreover, beside a direct effect in ROS production, KD also stimulates antioxidant protein catalase whose expression is stimulated by activated Peroxisome proliferator activated receptor  $\gamma$ 2 (PPAR $\gamma$ 2) transcription factor [74]. Here, PPAR activation occurs after histone hyper-acetylation following the inhibition of histone deacetylases (an epigenetic regulation) [75,76]. In turn, PPAR upregulates antioxidant genes as well as downregulates pro-inflammatory genes (NFKappaB, cyclooxygenase 2, iNOS) [77]. Histone deacetylase inhibitors are used as anti-inflammatory and anti-epileptogenic molecules [78]. Interestingly, ketone bodies are shown to inhibit histone deacetylase, although the precise mechanism is still to be determined [79].

Finally, Rahman et al. hypothesized that ketone bodies neuroprotection could rely on the G-protein coupled receptor GPR109 recently identified and who is activated by ketone bodies and found in the brain. Moreover, mice fed a KD or infused with ketone bodies show a decreased of ischemic infarcts dependent on GPR109. Further, authors show that 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 reduce seizures [80,81]. Finally, the anti-inflammatory role of ketone bodies inhibits NLRP3 inflammasome assembly through the blockade of K<sup>+</sup> efflux. However, the precise mechanism remains to be elucidated [82].

### 3.2. Stroke

Vegetarian diets (low GI and GL) are described to lower the risk of stroke [83,84] (Table 3). Therefore, a relationship between GI/GL and stroke could likely exist. On the other hand, a high fructose diet that should have a high GI worsens the post ischemic brain injury in rats [85]. In this later study, the authors highlighted an important effect in the hippocampus with increased inflammation while neuronal plasticity is decreased in parallel of neuronal loss. These changes lowering neuronal performances during ischemia recovery compared to normal chow fed mice. These results support a role of diet during the recovery period following a stroke. Here as well, glucose level is at play during the acute stage of a stroke and the recovery period. Thus, diabetes is a risk factor for stroke [86,87]. The oxidative stress associated with hyperglycemia is expected to be the mechanism involved in the poor outcome following a stroke. This suggests that a better glucose level control could help decrease the risk of stroke [88]. Diet interventions studies have provided interesting results in this regard. Thus, a high GL diet is associated with poor outcome in patients with acute ischemic stroke [89]. Recently, Song et al. found that in diabetic patients, this poor outcome does not depend on diabetes, but only on diet effect on glycemic variation. Furthermore, the authors suggest that the 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 [90,91]. One possible explanation is the cerebral hypo-perfusion or edema associated with hyperglycemia that lead to poor recovery from stroke [92,93]. Moreover, stroke is often linked to cytotoxicity whose association with hyperglycemia dampens the recovery [94]. In addition, mitochondrial dysfunction due to lactate production from glucose metabolism has also been suggested. Here, the lactate acidifies the intracellular environment and triggers the mitochondrial dysfunction [95]. Rapid increase in blood glucose also leads to oxidative stress and endothelial dysfunction observed in diabetes [96]. Further, high increases followed by periods of low levels are more deleterious than a continuous raise. Interestingly, high GI/GL increases glucose transiently, and thus have a negative effect on stroke outcome. Indeed, a dysfunctional endothelium has been described as a negative factor for acute ischemic stroke outcome [97]. Moreover, high GI/GL diets induces insulin resistance [31], that will increase serum levels of fibrinogen and von Willebrand factor (endothelial function) that would

increase the risk of stroke [98,99]. Thus, high GI/GL should induce hypercoagulability and increased risk of thrombosis. This phenotype is paralleled by an increase in small vessel diseases that could impair the stroke outcome [100]. Finally, in a cohort of Chinese women followed for 10 years, a positive association between GI and the risk of stroke observed supports the previous hypothesis [101]. Furthermore, the low GI Mediterranean diet is associated with a reduction in risk of stroke [102]. Finally, Lim et al. studied the role of diets in stroke recovery and cognitive impairments. In their study, the authors described that glycemic variability with hyperglycemic episodes is detrimental to cognitive function recovery. Thus, a diet avoiding amplitude oscillations for glycaemia is more suitable for both vascular and cognitive function recovery after a stroke [103].

Overall, evidences indicate that high glucose raise induced by the diet impacts both the risk and the outcome of stroke. The mechanisms in play are related to mitochondria and inflammation, as well as hyper coagulation. Moreover, chronic, and rapid hyperglycemia following a meal are deleterious for both risk and outcome. Thus, a low GI that induce a sustained elevation in blood glucose, should be beneficial for recovery after a stroke as well as decrease the risk of occurrence, by improving cardiovascular function.

### 3.3. Alzheimer's disease (AD)

Diets are widely used in AD to help delay or slow the development of the disease [104,105]. Also, AD relationship with metabolic disorders (insulin resistance) makes this disease considered as type III diabetes [106]. Therefore, nutritional approaches to study AD provided high insight in the brain function in the pathology related to diet changes. Recently, it was reported that a high GI diet increases the accumulation of Amyloid  $\beta$  ( $A\beta$ ) in brains from elderly, which is a marker of AD as well as a risk factor for the onset of the disease. In addition, these persons showed a cognitive decline, and Pet-scan imaging showed an increased association of  $A\beta$  accumulation with high GI diet [107] (Table 3). This interaction being independent of all other factors (age, sex, education), indicates that the high GI is highly involved in the  $A\beta$  accumulation in aging population and represents an increase risk factor for AD. In support of a key role of diet in AD onset, a high fat diet (HFD) induced insulin resistance increases brain  $A\beta$  accumulation. However, mice deleted for IRS2 (insulin signaling) become insulin resistant but do not accumulate  $A\beta$ , unless fed a HFD. Others also show that  $A\beta$  accumulation is accompanied by pTau aggregation (characteristic of AD) in insulin resistant AD mice model. Finally, oxidative stress and inflammation is described in this mice model [108].

Overall, these results indicating that the  $A\beta$  burden is related to diet confirms that nutritional adjustments could help prevent AD onset and slower its progression [109]. In support, a recent review describes that a healthy diet can decrease the risk of AD by lowering the oxidative stress and dampening the  $A\beta$  accumulation [110]. Moreover, this review discusses the anti-inflammatory effect of the healthy diet. In AD, inflammation is caused by the  $A\beta$  accumulation that stimulates the recruitment of microglia and astrocytes in parallel of interferon gamma ( $IFN\gamma$ ), interleukin  $1\beta$  ( $IL1\beta$ ) and tumor necrosis factor  $\alpha$  ( $TNF\alpha$ ) secretion [111,112].

AD is characterized by a decreased glucose uptake and utilization by brain cells. However, brain of AD people can still use ketone bodies [113,114]. Thus, KD could be used in AD to slow the disease progress or to delay the cognitive deficit. Medium chain triglyceride diet (MCT diet) is a diet less restrictive in carbohydrate but still ketogenic used in AD [114]. The low content in carbohydrate forces the organism to use lipid oxidation as energy source which also produce ketone bodies. Therefore, such diets have a low impact on glycaemia making them low GI diets. Brain energy metabolism and glucose uptake decrease are accompanied by mitochondrial dysfunction in AD [114]. Brain cells increased utilization of ketone bodies during brain energetic deficiency opened up to a new "neuroketotherapeutic" strategy to compensate the lack of glucose as energy source [114]. Beside this energetic role, ketone bodies are also involved in neurotransmission, or reduction of oxidative stress and inflammation relevant for AD. Ketone bodies involves the mitochondria and functional changes of it. As AD is associated with mitochondrial dysfunctions [115], ketone bodies could thus improve the disease phenotype. KD is also shown to increase the mitochondria number in the



hippocampus, which could contribute to the improvement of AD [116]. Furthermore, since ketone bodies produce less ROS than glucose, it can participate to a decrease the oxidative stress in AD [117,118]. This decrease in ROS production could be by stimulating uncoupling proteins (UCP) expression as shown previously [119,120]. Another possible mechanism is by both reducing glutamate transport and improving GABA activity that will decrease the excitability of neurons and thus ROS production (see paragraph 3.1). In addition, KD was shown to upregulate antioxidant proteins (MnSOD, Glutathione, Nrf2) [114]. 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 [121–125]. In support of a benefit of KD diets, mice models of AD also show decreased A $\beta$  accumulation in the brain when fed a KD [114], while in humans, the Medium Chain Triglycerides (MCT) diet have given encouraging improved memory or at least stabilization of cognitive function in AD people [114]. The direct effect of a KD in humans has been summarized by Taylor et al. who describe an improvement of almost all the memory and verbal communication tests in AD patients under a KD [114] (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 stimulates gene regulation. However, KD display important side effects. Therefore, more research should help better understand the mechanisms at play, and eventually develop a therapeutic approach targeting these mechanisms. Moreover, other low GI diet could have similar beneficial effect than KD, and thus must be tested. Overall, although there is solid evidence for ketone bodies involvement, the diets used in AD have several other effects that could be involved. Therefore, more research to understand the role of low GI on AD phenotype could help develop an adapted diet to the disease.

For instance, the Mediterranean diet (MD) is also protective against cognitive decline in AD [105]. MD is characterized by a high intake of vegetables, legumes, fruits and cereals, extra virgin oil (unsaturated fatty acids), low intake of saturated fats, meat, and a moderate intake of fish, a low to moderate intake of dairy products and amount of wine during meals [126,127]. MD is low in carbohydrates, while high in fibers, and so can be classified as low GI diet (Table 2). MD is known for numerous health benefits in cardiovascular or metabolic diseases, but also on cognition (lower decline) and to reduce the risk of dementia or AD [128,129]. Furthermore, people with mild cognitive impairment fed a MD show a decreased risk of AD onset, and improved memory, delayed recall, and global cognitive function [126]. Different studies suggest antioxidant, anti-inflammatory, cognitive function enhancement depending on nutrients components. For instance, the olive oil as a main source of fats enriched in omega-3 and phenolic acid is considered a main factor [126]. Olive oil decreases glycemic response to a high GI meal [130]. As such, olive oil helps lower the GI of a meal, and so decrease the glycemic increased induce by a meal that could participate to the effects observed. In addition, since the carbohydrate content of MD is low or non-digestible, ketogenesis is expected and repeat the action described above. Accordingly, a modified Mediterranean-ketogenic diet is described as associated with changes in AD biomarkers in CSF, suggesting that ketone bodies could be involved [131]. In addition, the observed changes in brain could result from gut microbiota alteration. 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 produces propionate or butyrate (Short Chain Fatty Acids (SCFA)). In turn, these SCFA have brain effects via histone deacetylase, transcription factor or antioxidant regulations. All of these effects will then provide neuroprotection and therefore protects against neurodegenerative disorders [132]. On the other hand, western diets containing processed food and carbohydrates decrease the number of bacteria producing SCFA. By so, these diets would have deleterious effects on brain and cognition. Interestingly, high processed food will most likely have a high GI while dietary fibers are low GI carbohydrates, indicating that low GII food are protective against neurodegenerative diseases.

The Gut-Brain axis and nutrition are also shown to participate in the pathophysiology of Autism Spectrum Disorder (ASD) [133]. Moreover, Parkinson 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...

Metabolism is often associated with brain pathological conditions. Thus, AD as well as PD risk increases with malnutrition and insulin resistance, while diet control is protective (138). Furthermore, insulin is shown to increase dopamine transporter mRNA levels in the substantia nigra [134]. Thus it is assumed that the high GI/GL diet could prevent PD by inducing high insulin secretion [135] (Table 3). However, this study suggesting a role for insulin is controversial since high GI induces insulin resistance while low GI improves insulin sensitivity [31]. Nonetheless, the population studied presenting a lower rate of PD while dieting high GI food such as rice, it is likely that other dietary factors could be involved. Indeed, Japanese diet is considered a healthy diet contributing to the expanded life expectancy observed in Japan. Thus, cardiovascular related death and neurodegenerative diseases rates are amongst the lowest in the world [136]. Japanese diet is characterized by raw ingredients used in meal preparation. The diet is low in fat and calories because most of the food used are vegetables, fish, meat, and rice, providing an excellent nutritional balance. This diet is low on 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) [135]. Therefore, the observed decrease in PD in the study of Murakami et al. could be due to improved insulin sensitivity rather than increased insulin levels. It was also described that high fat (high GI) diet is responsible for a decreased dopaminergic neurons in the substantia nigra due to a reduced PPAR and inflammation. Thus a low fat diet such the Japanese meals could prevent these PPAR and dopaminergic neurons decreases and protect against PD [137]. MD is also associated with 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 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 MD. Indeed, SCFA can improve insulin sensitivity, reduce inflammation, and stimulates Brain Derived Neurotrophic Factor (BDNF) production, that will help protect against PD. Another possible mechanism is through the antioxidant rich content of the MD. To note, some of the antioxidant products in the diet can also stimulate SCFA production, reinforcing the role of these molecules in brain function and pathology [138]. In support of that, SCFA concentration in feces of PD patients is decreased compared to control individuals [139]. However, Shin et al. also observed an increase of plasma SCFA correlated to the PD severity [140]. This result suggests a putative SCFA leakage from intestinal lumen to the bloodstream. Nevertheless, further studies are needed to clearly address the impact of SCFA on PD, and more generally of diets.

Depression and anxiety are other brain diseases that show a relationship with energy homeostasis [141,142]. Furthermore, depression has been studied in relation to GI/GL [143]. Although results are inconsistent, it seems that high GI/GL diets increase the risk of depression as well as aggravate the score of the disease [143] (Table 3). Rodent studies showed that HFD impaired 5-HT neurotransmission which increases anxiety behavior. The same group also reports a decreased anxiety following Connexin 43 down regulation or phosphorylation, or treatment with metformin (activator of AMPK) [144–146]. 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 with glutamate transport between intracellular to extracellular medium [147]. It was also observed that metformin decrease of BCAA is due to the inhibition of ketones derived BCAA production [148] suggesting that ketone bodies could be involved in depression and anxiety. Interestingly, in addition to ketones, anxiety and depression has been associated with oxidative stress, inflammation, and gut-brain communication [149,150]. Moreover, drugs are

developed to target the glutamate signaling and its recycling in the synapse [151]. Therefore, it is likely that diet intervention could involve similar processes than the ones described above.

Autism Spectrum Disorder (ASD) is a neurological condition associated with behavioral and social interactions defects that shows energy homeostasis dysregulation [152]. In fact, type 2 diabetes or obesity during pregnancy are risk factors for ASD in the offspring [152,153]. Chronic inflammation observed in metabolic disorders, and the immune system activation during pregnancy appears to be key in the risk of ASD [154–156]. Noteworthy, chronic inflammation can be decreased by low GI diet in obese subjects [157]. On the other hand, high GI diet increases advanced glycation end products (AGEs) that are involved in inflammation during obesity and diabetes. Indeed, AGEs activation of specific receptors result in C Reactive Protein (CRP) production and oxidative stress [158,159]. In support of this possible mechanism, Currais et al. demonstrate that mice offspring from high GI fed parents shows increased brain inflammation, reduced neurogenesis and ASD characteristic behaviors [160]. Dietary strategies have triggers improvement of ASD phenotype after birth. For instance, KD given to a mice model of ASD improve the social behavior and decrease repetitive behaviors [161]. In another attempt, gluten free foods decreased inflammatory grade and improved the ASD phenotype. However, only part of the subjects shows improvement, while others fail to observe a benefit [162,163]. These different studies using 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 in both the understanding of ASD brain alterations and diet interventions to determine the role of specific nutrients or metabolic products needs be done.

Microbiota is also associate with ASD behaviors [133,164,165]. Even if the role of gut microbiota is poorly understood, amino acid metabolism and inflammation are possible mechanisms participating to the phenotype observed. Low GI diet induces changes in microbiota are associated with ASD improvement. Thus, a participation of a product of low GI carbohydrates could be important. Finally, ASD mice model shows decreased blood levels of methionine also described in humans [166–168]. Interestingly, high GI diet also decreases the methionine levels [160]. Methionine is a precursor for DNA methylation and gene regulation [169]. In comparison, low GI diet maintains higher levels of methionine, suggesting that diet could improve ASD through epigenetic regulations. In line with microbiota role and low GI, sulforaphane, produced from low GI vegetables (cauliflower, broccoli), has been identified as a putative treatment in ASD. Indeed, sulforaphane given to autistic children improve their behavioral phenotype. Moreover, although the mechanism of action is not known, sulforaphane is described as modulating 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 low GI diet in ASD. Noteworthy, like for other neurological conditions, ASD improvement through diet is linked to oxidative stress, gene regulation and inflammation. Moreover, 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 useful in other neurological diseases (Table 3).

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



Although most of the mechanism described appears common to the diseases described and linked to diet interventions changes, no precise 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. Thus, more studies to determine the diet involvement in the production of these molecules should be done to determine precise diet recommendation. Thus, neurological disorders are likely to be successfully targeted by nutritional therapies.

#### 4. Glycemic index and brain regulation of energy homeostasis

GI/GL values predict the impact of food on metabolic response such as blood glucose and insulin levels. Thus, a high GI/GL will induce a rapid and high increase in blood glucose and insulin, while a low GI/GL induce a slow and limited raise of blood glucose that slightly affects insulin levels. Due to those effects, diets based on low GI foods have been developed to help control weight and prevent cardiometabolic disorders [175,176]. However, studies to address GI/GL effect on weight loss or glucose management in diabetic people gave rise to contradictory results. Among others, differences are likely to be attributed to a range in GI values for the same food making food choice based on such criteria more difficult. In addition, GI only considers the carbohydrate content of food, while lipids, proteins and vitamins can also influence the metabolic impact of the food [177].

Brain consume a large part of glucose of the body for its activity and needs a constant supply [12]. Therefore, according to the “selfish brain” theory, the brain competes with the body for glucose. Thus, the brain sends a message to increase glucose availability when its activity increases for instance. Furthermore, the brain is overly sensitive to glucose availability, and responsive to changes in glucose supply [13]. Such sensitivity makes the brain a key regulator, not only for its needs, but to maintain a glucose level constant in the blood [15]. Blood and brain parenchyma glucose levels are linked through a transport across the blood brain barrier via GLUT1 [178]. While hyperglycemia decreases GLUT1 expression, a drop in blood glucose will stimulate the GLUT1 expression [179]. However, brain glucose level does not parallel blood concentration [180]. Thus, micro-dialysis experiments reveal brain to blood glucose ratio of about 0.5. Furthermore, this ratio decreases when blood glucose increases [181]. This observation could be the result of a decreased GLUT1 expression that limits glucose uptake by the brain. Altogether, these results indicate a tightly regulated glucose supply to the brain to prevent both hypo and hyperglycemia from reaching the brain.

Physiological conditions involve a complex inter-organ communication to keep body weight and energy homeostasis in a balanced state. Brain plays a crucial role by integrating information on body energy status and adapting food intake and energy expenditure via signals sent to peripheral organs [182]. Further, brain specific areas are involved in the sensing of glucose as well as hormone concentration changes (insulin, ghrelin, leptin...) [183]. In this regard, GI/GL is expected to act on brain control of energy homeostasis. However, little is known on the impact of high or low GI/GL on those mechanisms. Nevertheless, due to changes in blood insulin and glucose levels, changes in brain responses are likely to occur. Whether these changes are due to a direct (glucose or insulin level) or indirect (hormonal, nutrient or cytokine level change due to the meal) on brain control of metabolism should be determined. Moreover, the relationship between GI and metabolic disorders remain unclear despite several studies [184–188]. Intriguingly, the mechanisms involved in cognition or neurological disorders are described in brain energy homeostasis regulation. Thus, ROS signaling, mitochondrial activity, gut-brain axis and SCFA, ketone bodies, astrocyte-neuron communication, glutamate metabolism, or gene regulation and neurogenesis or plasticity have been involved in brain metabolic regulations.

Nevertheless, so far, only few studies tried to determine the impact of GI/GL on brain control of metabolism. However, nutrition can affect body weight, insulin sensitivity, adiposity, and other metabolic parameters. Thus, we will discuss here results suggesting GI/GL impact on brain control of energy homeostasis.

#### 4.1. GI/GL and brain glucose detection

Within the brain specific regions are dedicated to the sensing of signals involved in energy homeostasis regulation. The hypothalamus is the first area to sense these peripheral signals on the energy status of the body. Within the different nucleus forming the hypothalamus, various neuronal populations are well described [14]. Further, glucose sensing and the regulatory response to the periphery is well characterized in the hypothalamus [15]. This precise sensing of blood glucose is possible due to a blood brain barrier permeability weaker in this area of the brain. By such, the impact of foods on blood glucose level is directly integrated by the hypothalamus to restore euglycemia. In this regard, GI/GL should involve a hypothalamic activation of neuronal circuits of glucose and energy homeostasis regulations. Low GI food leads to a controlled increase in blood glucose level that is progressively returned to euglycaemia. In this case, insulin release is only limited, glucose level is decreased due to tissue utilization. On the other hand, high GI/GL results in a high increase of glucose levels in the first phase. Such rise in blood glucose would stimulate brain hyperglycemia detection. In turn, high glucose excited (HGE) neurons will be activated which will lead to the release of neurotransmitters (GABA in VMN and NTS or anorexigenic neuropeptides POMC/CART in the ARC) [189]. In a second phase, this should lead to a decreased blood glucose that would involve the same area but stimulates other neurons called glucose inhibited. The activation of these neurons occurs when glucose levels decrease. Following their stimulation, the brain will send adaptive signals to stimulate food intake and glucose production [190]. Brain sensing of a high glucose level will induce a peripheral response by inducing an insulin release by the pancreas [191]. This response contributes to the rapid decreased glucose level and the hypoglycemia induced. Following this second phase, the hypoglycemia detection is activated and involves the brain in contributing to stimulate food intake by activating orexigenic neurons.

Interestingly, redox balance is involved in both hyper and hypoglycemia sensing. Thus hyperglycemia induces mitochondrial ROS production in the hypothalamus. The inhibition of this ROS production inhibits the insulin secretion normally observed due to a lack of nervous activation [192]. In addition, changes in mitochondria morphology is necessary to finely regulate this ROS signaling [193]. During obesity and diabetes, it is observed a hypersensitivity to glucose. This hypersensitivity is characterized by insulin secretion by the pancreas after a detection of glucose level lower than the usual level inducing this response. This hypersensitivity is linked to dysfunctions of mitochondrial respiration activity. Consequently, ROS levels are higher than in the non-obese group. Finally, an antioxidant treatment to decrease the ROS level in the hypothalamus restores a normal glucose sensing function, demonstrating the redox balance importance [194,195]. Dysfunctions of mitochondrial dynamics and ROS signaling have also been shown during metabolic unbalance [196]. Hypoglycemia detection also depends on ROS signaling. Here, ROS are produced during normal hypoglycemic counter regulation. However, after recurrent hypoglycemic episodes, there is no ROS production [197]. These results support a key role of mitochondria and redox balance in hypothalamic regulation of energy homeostasis as also shown in other studies [198–202]. In addition, lipids, insulin, or ghrelin signaling in the hypothalamus also participate to ROS signaling. Therefore, according to the mechanisms putatively involved in low *vs* high GI diet, and its impact on ROS production (see paragraph 3), it is likely that hypothalamic regulation of metabolism will be affected by the GI of a food or diet. For instance, high GI diet could mimic a recurrent increase in RS and therefore disrupts the mechanism of hypoglycemia counter regulation. Also, recurrent increases in glucose and insulin could participate to the development of insulin resistance in brain as it is observed for high GI diet in peripheral tissues [31]. On the other hand, low GI diet would produce ketone bodies that are inhibitors of ROS production by interfering with the mitochondria respiration as described above [72–74,203–209]. Interestingly, ketone bodies have recently been involve in metabolic disorders and brain control of energy homeostasis notably by affecting food intake [203–209]. Discrepancies in results could be due to various parameters including the origin of ketone bodies. Indeed, high fat diet is associated with hyperketonemia induced by the increased in fat metabolism from diet, while fasting ketone bodies are produced from lipid stores in the body.

Therefore, results observed can be altered by other signals such as fatty acids, hyperglycemia, hyperinsulinemia, or leptin among others during high fat diet. High GI diet will probably fall in this situation since they are high in carbohydrate and high GI foods. Low GI diet, however, will induce a ketone bodies production from the fatty acids produced from adipose tissue. Moreover, in addition to ketone bodies produced in the liver, in this condition, astrocytes ketogenesis will be stimulated as well [210,211]. Indeed, it is possible that the signal by ketone bodies produced by astrocytes locally would be different from hepatic ketone bodies that would affect the whole body.

Ketone bodies could also be involve in metabolic through the acetylation or methylation of genes, thus modulating their transcription, as described before [75–77]. Indeed, such gene regulation has previously been linked to brain control of energy homeostasis [212–215]. Of particular interest, these processes have been involved in neurogenesis, brain plasticity and neuronal function. Therefore, the low GI diet produced ketone bodies should lead to changes in these mechanisms, and modify neural regulation of metabolism. Since ketone bodies are associated with fat metabolism, they would rather signal a lack of energy that would stimulate food intake or increase glucose supply. However, this assumption remains to be tested since others describe an inhibition of food intake by ketone bodies. Nevertheless, epigenetics mechanisms stimulated by low GI should help control energetic balance, while high GI would rather lower ketone bodies production and thus block their signal. However, further studies will be needed to completely understand the role of ketone bodies in brain regulation of energy homeostasis.

Interestingly, ketone bodies are involved in changes in ATP production. Such role was described in neurological disorders. Either ketone bodies by inhibiting glycolysis decrease the ATP production, or by forming substrates for the mitochondrial respiration maintain ATP production. Such hypothesis remain to be tested so far. Nevertheless, ATP levels would be responsible for regulation of  $K_{ATP}$  channel closure [65–68]. Such role of ATP production would then regulate the depolarization of GE neurons that are  $K_{ATP}$  dependent channels [216].

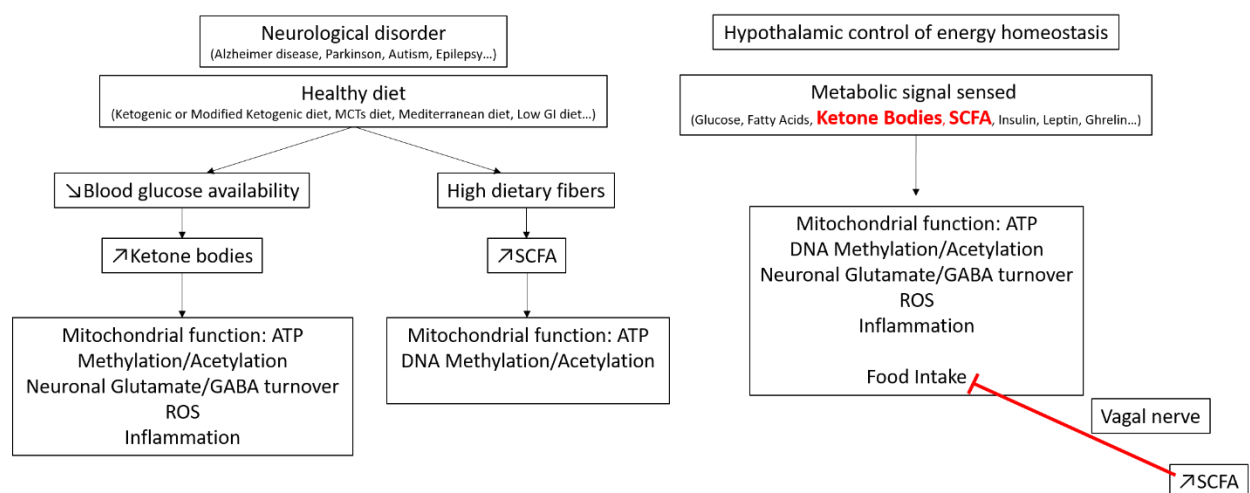
Astrocyte ketogenesis also supports a role for glial cells in energy homeostasis. First astrocytes provide energy to neurons to maintain a normal activity. Further, astrocytes play a role as a sensor of metabolic status, and signal this information to the neurons [217,218]. Therefore, astrocyte-neuron communication is key in the regulation of energetic signal transport and sensing by neurons. Indeed, studies describe the role of astrocytes in the detection of leptin, glucose, fatty acids or amino acids and their involvement in metabolic balance [219–224]. Astrocyte role in glutamate recycling also associates the lactate supply to neurons for neurotransmitter action [223]. In addition, disrupting the communication between astrocytes by blocking Connexin 43 protein that participate in the astroglial network in the hypothalamus, inhibits glucose sensing response. This result support an indispensable transport through astrocytes for normal glucose detection [225]. The astrocyte-neuron lactate shuttle theory (ANLS) hypothesizes that astrocytes metabolize glucose taken up from bloodstream, and then convert it into lactate in the glycolysis. The lactate produce is then transferred to neurons where it can be oxidized. Therefore, lactate would serve as signaling molecule for blood glucose level. Accordingly, lactate infusion to the brain mimics the response obtain with glucose [226]. Overall, glucose changes associated with ANLS and the glutamate recycling represent targets for GI diet producing ketone bodies following similar mechanisms described in neuronal disorders. However, such hypothesis has not been tested so far in the context of brain nutrient sensing.

Finally, gut-brain axis is also involved in brain regulation of energy homeostasis. In addition, diet composition and GI alter the gut function via microbiota that has an effect on neurological disorders [227–229]. Here, the same molecules identified in neurological conditions are also known to affect brain circuits of metabolic control. Indeed, dietary fibers are expected to provide resistance to metabolic disorders onset as well as the discuss effect on neurological disorders and cognition. Dietary fibers are found in low GI food such as vegetables [16]. Thus, the action of GI on microbiota will affect brain control of energy homeostasis via SCFA. Here, SCFA is describe to have a satiating

effect [37,230]. More recently, microbiota changes has been shown to activate POMC neurons (anorexigenic), reinforcing the role of gut-brain axis in food intake control [231]. Other works indicate that leptin sensitivity inhibition and pro-glucagon and BDNF decreases induced by microbiota changes could participate in obesity [232]. Interestingly, leptin sensitivity and BDNF are linked to AD, strongly suggesting that microbiota could be a key element in the relationship between brain disorders and metabolism. Therefore, the meal composition and the GI of the foods and the meal represent an interesting target in the elucidation of this relationship, but also to prevent, delay or treat the diseases.

## 5. Conclusion and Perspectives 9353

GI/GL values gave rise to new diets to help people with metabolic diseases to control their body weight and glucose homeostasis. Encouraging results on weight management and insulin sensitivity improvement have been observed. In addition, more historical diets such as ketogenic or modified ketogenic diets, Mediterranean diet, Japanese diet that are likely to have a low GI are associated with healthy lifestyle. In addition to their metabolic improvement properties, these diets also show positive effects on neuronal diseases. Thus, people following these type of diets present a decreased risk to develop brain diseases while aging. Furthermore, these diets are also used to treat epilepsy for example since decades. However, even knowing that these nutritional interventions improve wellbeing, little is still known on the mechanisms involved. Interestingly, despite a first role in metabolic control, the most important progress in the understanding of brain impact of low GI diet comes from neurological conditions studies. Nevertheless, it is worth to note that the mechanisms identified or hypothesized from these studies have been described in the context of brain control of energy homeostasis. Among these mechanisms, redox balance, mitochondrial function, ATP production, insulin sensitivity, gene regulation, astrocyte-neuron lactate shuttle, and neurotransmitters regulation are all involved (Figure2).



**Figure 2.** Schematic representation of the different mechanisms putatively involved in beneficial effect of low GI diet on neurological disorders (left panel), paralleled with known mechanisms involved in brain control of energy homeostasis (right panel).

Thus, these mechanisms appear to be key in brain function, and alteration of them could lead to neurological dysfunctions. These dysfunctions would then lead to neurological disorders or defect on brain regulatory mechanism such as energy homeostasis. Therefore, the inability of brain to precisely modulate energy needs for its own needs will triggers neurological dysfunctions.

However, better understanding of those mechanisms is still needed to completely understand both neurological disorders and metabolic disorders. Moreover, improved knowledge could help to decipher the increasingly evident relationship between neuronal disorders and metabolic balance.

Finally, a better understanding of the mechanisms involved diets could help develop and improve nutritional recommendation for improve health of people with those diseases. In addition, diet could be a good target to prevent development of both metabolic and neuronal disorders. In the end, deciphering how these mechanisms involved diets could come out from those studies to improve cognitive function in healthy people as well.

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