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Review

Dietary manipulation and caloric restriction in the development of mouse models relevant to neurological diseases

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ABSTRACT

Manipulation of diet such as increasing the level of fat or inducing insulin resistance has been shown to exacerbate the pathology in several animal models of neurological disease. Caloric restriction, however, has been demonstrated to extend the life span of many organisms. Reduced calorie consumption appears to increase the resistance of neurons to intracellular and extracellular stress and consequently improves the behavioural phenotype in animal models of neurological diseases, such as Alzheimer's disease. We review the evidence from a variety of mouse models that diet is a risk factor that can significantly contribute to the development of neurological diseases.

1. Introduction

High calorie diet is a risk factor that can significantly contribute to the development of neurological disease. Conversely, calorific restriction has been shown to reduce symptom progression of neurological disorders, such as AD, suggesting that diet management is of significant importance to prevent or reduce the prevalence of neurological diseases in the developing society. Importantly, this key concept has been successfully recapitulated in mouse models of neurological disease, where dietary manipulations performed on mice exhibiting "AD-like" pathology, for example, have identified critical mechanisms/targets that contribute to, or potentially reduce the development of disease and hence offer novel therapeutic strategies relevant to disease prevention. This review will provide further evidence to the clinical and epidemiological evidence linking high fat diet to the risk of neurological disease by direct evidence resulting from data generated in mouse models of disease. These studies have elucidated novel mechanisms and targets that are regulated in response to dietary manipulations and evaluating such targets and pathways should provide future therapeutic opportunities for patients.

2. Dietary modulation

Numerous studies implicate certain cardiovascular risk factors as key triggers for the onset and development of vascular-related dementia [1]. Increasing evidence has confirmed that abnormal levels of cholesterol, or detrimental cholesterol metabolism, play a pivotal role in the pathophysiology of Alzheimer's disease (AD). Epidemiological and clinical studies have indicated that patients with elevated levels of cholesterol have an increased susceptibility to AD [2] and AD is more prevalent in countries with high-fat and high-calorie diets [3]. Furthermore, a large body of evidence indicates that dietary conditions that promote the development of insulin resistance (IR) may also increase the relative risk of AD. Importantly, epidemiological studies suggest that IR as a consequence of Type II diabetes (T2D) characterized by glucose intolerance, obesity and hyperinsulinemia is associated with a 2- to 3-fold increased relative risk of AD, independent of the risk for VaD [4,5]. These concepts have become more poignant to date due to the rising prevalence rates of T2D, obesity and AD over the last few decades. Approximately 24 million people worldwide are now reported as having dementia, with the prevalence rate predicted to double every 20 years [6]. Although ageing is regarded as the strongest risk factor for developing AD, emerging evidence suggests that dyslipidemia and T2D can contribute significantly to the pathogenesis of AD either via direct or indirect mechanisms. Animal models relevant to AD in combination with dietary manipulation have effectively supported this hypothesis and have identified genes, targets and pathways that may be suitable for future therapeutic intervention. Importantly a number of other neurodegenerative disorders have been associated with impaired

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insulin sensitivity and metabolic dysfunction e.g. Huntington's disease, Down's syndrome, Friedreich's ataxia, etc. [7], although appropriate mouse models have not be rigorously evaluated to determine the contribution of dietary manipulations on glucose metabolism and progression of disease in relation to these syndromes. However, AD-relevant mouse models have been used more extensively to address the impact of dietary modification on disease and have provided useful insights into potential targets and pathways which may have broader utility for other neurodegenerative/neurological diseases. The next sections of this review will document the evidence obtained from mouse models which highlight the contribution of dietary modulation on pathophysiological and neurological end-points relevant to AD and identify potential opportunities for treatment.

Preclinical evidence for supporting a role for abnormal cholesterol metabolism in the pathogenesis of AD was initially confirmed through the use of hemizygous double mutant PSAPP mice, derived from crossing hemizygous transgenic mice expressing familial AD human mutant $APP_{KG70N.M671L}$ (Tg2576 line) [8] with a homozygous line of mice expressing the human familial mutant $PS1_{M146V}$ (line 8.9) [9]. From 5 weeks of age, mice were either placed on a high-cholesterol diet (containing 5% cholesterol, 10% fat, and 2% cholate and 5.2 kcal/g) or a basal diet (containing 0.005% cholesterol and 10% fat and 3.6 kcal/g) for 7 weeks [10]. The results from the study demonstrated that diet-induced hypercholesterolemia in PSAPP transgenic mice elevated both plasma and CNS cholesterol levels as well as increasing the accumulation of Aβ in the CNS, relative to the basal diet. Importantly significant elevations in Aβ were measured by three independent techniques (ELISA, IP/MS and IHC) and total Aβ (ELISA) correlated positively with both increases in plasma and CNS cholesterol. The hypothesis generated from this pivotal study implicated that abnormal cholesterol levels/metabolism either increase APP processing or APP sorting which may have contributed towards accelerating AD-relevant Aβ pathology in this transgenic line of mice. These findings were subsequently confirmed in an APP695 (K670N and M671L) Swedish mutant mouse model of AD fed a high fat/cholesterol diet for 7–10 months [11]. A more recent study [12] attempted to evaluate the role of hypercholesterolemia on neuroinflammation and APP processing in normal C57BL/6 mice and low-density lipoprotein receptor (LDLR) deficient mice and to determine the functional consequences of this dietary manipulation via cognitive testing. Essentially each of the two strains of mice either received normal chow (5% fat and 0.05% cholesterol) or high-fat/-cholesterol (21%/1.25%) diet at 4 months of age for a period of 2 months. Mice were evaluated in the 8-arm radial maze for cognitive performance in the last 2 weeks of the 2 month dietary regime and then brains were harvested to determine markers of neuroinflammation together with Aβ. The results from this study confirmed that a high-fat/-cholesterol diet for 2 months increased plasma levels of both total and LDL-associated cholesterol which was associated with working memory impairments in both C57/BL6 and LDLR-deficient mice. Importantly the LDLR-deficient mice showed a working memory deficit regardless of diet, suggesting the targeted disruption of the gene which induces a moderate hypercholestolemia was sufficient in its own right to contribute towards inducing a cognitive deficit. Immunohistochemical analysis revealed significant microglial (CD45+ve) and astrocytic (GFAP+ve) activation within the hippocampi of both C57/BL6 and LDLR-deficient mice fed a high-fat/-cholesterol diet together with increased cytokine (TNFα, IL-1β, IL-6) and iNOS and Cox-2 gene expression (via qRT-PCR). Interestingly increases in APP processing (BACE1 expression and generation of APP CTFs) were also apparent in both C57/BL6 and LDLR-deficient mice fed a high fat/cholesterol diet. Importantly, these results further support the significant contribution played by the adverse effects of a cholesterol-rich/high fat diet on pathophysiological markers relevant to AD and confirm the consequent memory impairments in a non-familial AD mouse model. Clearly mouse models have contributed to our improved understanding for the role of abnormal cholesterol metabolism in developing cognitive impairments and neuropathological processes relevant to disease and may offer an appropriate test bed to evaluate novel therapeutic strategies (beyond statins (HMG-CoA reductase inhibitors) which have provided mixed results in AD clinical trials) targeted to reduce hypercholesterolemia [13,14].

The concept of diet-induced insulin resistance or abnormalities in insulin metabolism directly contributing to the progression of symptoms and amyloidosis, relevant to AD, was elegantly demonstrated in a pivotal study using Tg 2576 mice [15]. Essentially 3- to 4-month-old female Tg2576 mice were exposed to a high-fat (60% fat, 20% carbohydrate, 20% protein) dietary regime for 5 months relative to standard laboratory diet (10% fat, 70% carbohydrate and 20% protein). Importantly both diets contained equal percentages (0.03%) of cholesterol per gram of diet. At 9 months of age the Tg2576 mice that had been administered the high-fat diet developed insulin-resistance (impaired glucose tolerance, increased serum insulin content and body weight/ependymal fat pad weight) relative to age-matched Tg2576 exposed to the control diet. Insulin-resistant Tg2576 mice were also shown to be significantly impaired in the acquisition phase of the Morris water maze, highlighting deficits in spatial learning relative to age-matched normoglycemic Tg2576 mice. Furthermore, the high-fat diet promoted a >2 fold elevation in Aβ 1–40 and 1–42 peptide species (measured by ELISA) in the hippocampus of Tg 2576 mice which was accompanied by a ~2 fold elevation in cortical Aβ (6E10-immunopositive) plaque burden. An interrogation of the potential mechanisms involved with diet-induced insulin resistance in Tg2576 mice identified selective alterations in brain insulin receptor signalling, namely reductions in: insulin-receptor-β activation; the content of PI3K p85 subunit expression; pS^{473}-AKT/PKB phosphorylation (reduction in AKT/PKB activation) and pS^{21}-GSK3α/pS^{21}-GSK3β phosphorylation (indicative of increased GSK3α and GSK3β activities). Intriguingly the authors further demonstrated that the level of pS^{21}-GSK3α and pS^{21}-GSK3β activation was strongly correlated with the generation of the brain CTF-γ cleavage product of APP (an index of γ-secretase activity), suggesting that insulin resistance (via a high fat diet) may promote the generation of Aβ in the CNS. Finally, a significant reduction in insulin-degrading enzyme (IDE) activity and membrane-associated IDE protein content was observed in the cortex of Tg2576 exposed to a high-fat diet potentially implicating a reduction in the degradation of Aβ via inhibition of IDE activity/expression in the CNS. As a follow-up study this research group [16] then went on to demonstrate an increased expression of connective tissue growth factor (CTGF) in the CNS of Tg2576 mice exposed to a high-fat diet correlated with an increasing Aβ plaque burden. Importantly Zhao et al., [16] showed that the CTGF gene (also known as insulin growth factor binding protein IGFBP and which has been implicated in the pathophysiology of diabetes) was elevated together with protein in the brains of different strains of mice (129/svJ and Tg2576) with established diet-induced insulin resistance and was shown to be increased in post-mortem AD brain as a function of clinical dementia and Aβ neuritic plaques. These results suggest that CTGF expression in the CNS may significantly contribute to Aβ pathogenesis and cognitive deficits via a mechanism induced in response to insulin resistance. Therefore this diet-induced insulin-resistant AD-relevant mouse model can be viewed to provide a simple yet physiologically relevant system for evaluating the pathophysiological mechanisms relevant to insulin-resistance and importantly offers the opportunity for assessing novel therapeutic strategies associated with insulin and GSK-3 signalling pathways.

Although Tg2576 mice are susceptible to diet-induced insulin resistance and the development of exacerbated cognitive deficits and Aβ load and plaque burden, there is evidence to suggest that this APP mouse line develops insulin-resistance with age without any high fat dietary manipulation. For example, Pedersen and Flynn [17]

demonstrated that male Tg2576 mice at 13 months of age become hyperinsulinemic following an overnight fast and this insulin-resistant phenotype is effectively reduced to wild-type control levels via the administration of the PPARγ agonist rosiglitazone (following 4 months of drug treatment in the diet from 9 months of age). Rosiglitazone-supplemented diet significantly reduced the learning and memory deficits in Tg2576 mice at ~13 months of age using the 8-arm radial maze, a task requiring engagement of the hippocampus and cortex and the regions which show the most severe pathology [18]. Continuous treatment with rosiglitazone up to ~16 months of age, significantly reduced Aβ1-42 levels in the frontal cortex (via ELISA), increased IDE gene expression in hippocampal regions (via in-situ hybridization) and attenuated the reduction in IDE activity in the frontal cortex (^{125}I-insulin degradation). These results suggest that improving peripheral and/or central insulin sensitivity may enhance cognitive function and reduce Aβ pathogenesis in a transgenic mouse model of AD which exhibits an insulin-resistant background. Importantly these results have some clinical relevance, in that an alternative PPARγ agonist pioglitazone has recently been shown to improve cognitive function in mild AD patients with T2D, suggesting that improving insulin-sensitivity/signalling may offer therapeutic promise in an enriched (insulin-resistant) sub-population of AD patients [19].

The utility of the triple-transgenic mouse model (harboring PS1M146V, APPSwe, and Tau P301L transgenes: 3× Tg) has greatly facilitated basic research in uncovering novel mechanisms/targets which contribute to accelerated cognitive deficits, amyloidosis, and the phosphorylation of tau relevant to AD [20]. Interestingly, a less aggressive line of 3× Tg mice fed a diet high in saturated and omega-6 fat together with cholesterol for 4 months (from 5 months of age) increased c-jun N-terminal kinase (JNK) activation, phosphorylated insulin-receptor substrate 1 (IRS1) and tau relative to control diet [21]. JNK activation, IRS-1 and tau phosphorylation have been reported to uncouple insulin signalling which may in part contribute to a reduced glucose metabolism and utilization consistent with an insulin resistant phenotype. Interestingly the authors also noted that if 3× Tg mice were exposed to a high-fat diet and were supplemented with fish oil/DHA (docosahexaenoic acid/polyunsaturated fatty acid) or curcumin (a NF-κβ and JNK inhibitor/polyphenolic anti-inflammatory agent) or a combination or both for 4 months significant reductions in phosphorylated JNK, IRS-1 and tau together with an improvement in working-memory cognitive performance (using the Y-maze) was demonstrated [21]. The results from this study suggest that pleiotropic effects involving multiple pathways contribute to insulin-resistance and targeted interventions towards anti-inflammatory and anti-oxidant pathways may offer potential disease-prevention and symptom improvement in AD patients. Diets enriched in DHA have previously been shown to reduce amyloid burden in aged Tg2576 mice [22] and importantly epidemiological studies suggest an increased intake of omega-3/DHA can reduce the risk of developing AD [3,23].

Another dietary manipulation in mice, intake of sucrose-sweetened water, has recently been shown to induce insulin-resistance and exacerbate cognitive deficits and amyloidosis in the APP/PS1 transgenic mouse model of AD [24]. Exposure of 10% sucrose-sweetened water or water ad-libitum on a background of a low-fat rodent diet for 25 weeks to 2 month old APP/PS1 mice resulted in increased weight gain (through increased total calorific intake), impaired glucose tolerance and increased fasting plasma insulin and lipid (total cholesterol) levels indicative of an insulin-resistant and hypercholesterolemia phenotype. Furthermore, spatial learning and memory deficits were apparent in the APP/PS1 transgenic mice exposed to sucrose-sweetened water and a 2- to 3-fold increase in total Aβ42 levels (ELISA) and plaque deposition were observed in the CNS. No effects on APP transgene expression were shown but a reduction in IDE (30%) and an increase in ApoE (2.5 fold) levels were observed in the brains of these mice. The authors hypothesized that exacerbation of cerebral amyloidosis in sucrose-treated APP/PS1 mice resulted mainly from an increased aggregation of Aβ induced by the up-regulation of murine ApoE which has been shown to promote aggregation and fibril formation of Aβ. These results implicate the chronic consumption of sugar-sweetened beverages could lead to insulin-resistance independent of dietary fat intake and has clinical relevance to obesity and cognitive impairments associated with neurological diseases such as AD. Based on the findings of this mouse study and clinical and epidemiological literature [25,26] appropriate management of excessive consumption of sugar-sweetened beverages may help to offset the development of cognitive deficits and risk associated with the progression of AD.

A recent study employing of the TgCRN8 (harbouring 3 mutations in the APP gene i.e. K670M/N671L and V717F) mouse model of AD evaluated the effects of different dietary compositions on cerebral amyloidosis and neuronal integrity [27]. Essentially 4 different diets composed of either high fat/low carbohydrate, high protein/low carbohydrate, high carbohydrate/low fat or reference chow were compared for effects on Aβ load and plaque deposition together with assessment of neuronal density and volume in the hippocampus from 4 weeks of age. Following 18 weeks of exposure to the diets, TgCRN8 mice treated with the high-fat/low-carbohydrate diet exhibited the highest levels of solubilized Aβ42, although this did not translate into elevated plaque burden. Importantly body weights were significantly elevated from week 6, where high fat/low carbohydrate induced the highest weight gains in TgCRN8 mice and this profile continued to the culmination of the study at 18 weeks. No overt differences were shown in markers of neuronal density or volume with each of the diets, although the high protein/low carbohydrate diet induced reductions in brain weight and a tendency for reduced density and volume in the CA3 hippocampal region of TgCRN8 mice. Unfortunately non-transgenic mice were not incorporated into the study design so it is difficult to draw too many conclusions, although the high-fat/low-carbohydrate diet consistently elevated body weight and Aβ levels consistent with other transgenic mouse models of AD.

As a means to truly test the direct role of neuronal insulin resistance, as opposed to peripheral insulin resistance via dietary manipulation, a study evaluating the effects of the neuron-specific insulin receptor knockout mouse (NIRKO) were performed [28] to determine mechanisms and targets that may have relevance to neurological disorders which harbour an insulin-resistant phenotype e.g. AD, and may support the concept of a 'brain' type 3 diabetes [29]. Importantly NIRKO mice exhibited a complete loss of insulin-mediated activation of PI3-kinase and markedly reduced phosphorylation of Akt and resulting increased phosphorylation of GSK3β leading to significant phosphorylation of tau, a key neuropathological hallmark of AD. Although this study went on to confirm no loss of neuronal integrity, motor or cognitive impairments or CNS glucose metabolism (via [^{18}F]FDG-micro PET) in the NIRKO mouse, the authors postulate that this model offers a direct link between dysfunctional insulin signalling in the brain and Akt, GSK3β and tau hyperphosphorylation. Unfortunately no measurements of rodent Aβ were conducted. Importantly this study suggests that although "neuronal" insulin resistance may be a contributory factor towards developing AD, additional factors may well interact to generate the clinical and neuropathological hallmarks of the disease. Further studies are required to determine how these other/multiple factors (e.g. over-expression of mutant APP and PS1, dietary manipulation) may interact with reductions in central insulin signalling to facilitate a more complete understanding of their relative contributions to cognitive impairment and neurodegeneration in mouse models of AD.

Impaired metabolic control has also been reported to be a risk factor for the development Parkinson's disease (PD), particularly at the onset of midlife adiposity [30] and abdominal obesity in non-smokers [31]. This epidemiological evidence has been supported by

the utility of mouse models of obesity (i.e. *ob*/*ob*, leptin-deficit spontaneous mutation and high-fat diet) through the administration of neurotoxins relevant to inducing dopaminergic terminal and cell death to effectively recapitulate 'PD-like' pathology. For example, Sriram et al., [32] demonstrated that when the dopaminergic neurotoxin methamphetamine was systemically administered to female C57BL/6J Lep^{ob} (*ob*/*ob*) mice at 4–6 months of age, significant mortality was demonstrated compared to lean litter mate controls. Furthermore, methamphetamine was shown to significantly exacerbate the neurotoxic phenotype in ob/ob mice compared to lean litter mate controls, regarding reduced dopamine content, loss of tyrosine hydroxylase protein and an elevation of GFAP within the striatum. Importantly, methamphetamine was shown to increase mitochondrial uncoupling protein-2 (UCP-2) gene expression within the striatum of *ob*/*ob* mice relative to lean mice (>4.6 fold) suggesting that oxidative stress and mitochondrial dysfunction may critically contribute to the severe neurotoxic phenotype exhibited by *ob*/*ob* mice in this study. More recently, high-fat diet induced obesity has been shown to enhance the susceptibility of the dopaminergic cell death and oxidative stress to the classical parkinsonian neurotoxin 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in mice [33]. Importantly, the high fat diet (modified AIN-76A diet with 40% beef tallow) administered for 8 weeks to C57BL/6 mice significantly decreased levels of striatal dopamine in addition to the reduced content of tyrosine hydroxylase and microtubule-associated-protein within the substantia nigra following subtoxic doses of MPTP, compared to a matched lean group of mice. Interestingly, the levels of nitrate/nitrate (NOx) were elevated in both plasma and substantia nigra, while thiobarbituric acid-malondialdehyde adducts were suppressed within the substantia nigra of obese MPTP-treated mice, suggesting a systemic inflammatory and central oxidative stress/mitochondrial dysfunction phenotype was observed under these conditions. Furthermore striatal nNOS phosphorylation and dopamine turnover were increased, while nigral Mn-SOD expression and activity were reduced in obese mice after MPTP treatment, but this phenomenon was not present in lean mice. Exploration of higher doses of MPTP increased the mortality rate in obese mice, relative to lean mice suggesting a reduced tolerability to oxidative stress. These results suggest that diet-induced obesity may increase the vulnerability of dopaminergic neurons and terminals to neurotoxins such as MPTP, through enhanced reactive oxygen and nitrogen species generation with a reduced anti-oxidant capacity. Taken together these two mouse studies provide supporting evidence to previous epidemiological studies suggesting a link between obesity/metabolic stress, dopaminergic dysfunction and Parkinson's disease, although further studies are required to corroborate this hypothesis.

When comparing data across neurological mouse models that have incorporated dietary manipulation (high fat diet), it is important to consider whether the insulin resistant-like phenotype closely corresponds to classical genetic mouse models of T2D and obesity. For, example the *db*/*db* mouse model of T2D shows a progressive deterioration of glycemic control and insulin responsiveness, while the *ob*/*ob* mouse model represents an obese, hyperinsulinemic and insulin-resistant model which is less severe and viewed to be more stable than that observed in the *db*/*db* mouse [34]. Importantly when comparing the results generated from studies employing, for example, aged Tg2576 APP transgenic mice (e.g. [15] and [17]) with mouse anti-diabetic efficacy studies using *db*/*db* mice (e.g. [35]) appropriate markers such as serum/plasma insulin levels are very close in magnitude, suggesting comparative levels of insulin resistance. This evidence would suggest that both environmental and genetic factors may interact in a complex manner and pre-dispose enhanced susceptibility to insulin-resistance and the progression of disease. Clearly further work is necessary to determine how target pathways may overlap between T2D/obesity and 'AD-like' mouse models, for example, in order to determine a more definitive characterization of the causal triggers and contributory factors involved in the development of disease onset and progression.

In summary, dietary manipulations in mouse models of AD, and to some extent PD, have greatly supported the clinical epidemiological evidence suggesting a strong link between high fat/cholesterol and carbohydrate-rich diets, insulin resistance and the development of neuropathological hallmarks of disease. As will be covered in the next section of this review, resveratrol, a putative SIRT1 and AMPK activator, has been shown to improve insulin sensitivity and longevity in mice, particularly on an aged and high-calorific diet background [36]. Moreover, recent evidence suggests that a reduction in SIRT-1 (mRNA and protein) is closely associated with the accumulation of Aβ and tau in the brains of AD patients [37], making this target an attractive focus for further research. The concept of improving health and neurological diseases through diet management and/or via modulation of metabolic signalling through new chemical entities (NCEs) may have important consequences for society in the future, particularly as obesity, T2D and diseases of ageing are developing at such a rapid rate.

3. Caloric restriction

Caloric restriction (CR) is the reduction of the average calorie intake to 50% - 70% of the calories consumed by humans and animals ad libitum (AL). Its beneficial effects on age related diseases and indeed aging itself have been postulated for over 60 years [38]. Vice versa there is mounting evidence that high-calorie input and lack of exercise are major risk factors for various age-related diseases including diabetes, cardiovascular diseases and cancer. This highlights the importance of maintaining metabolic balance on various aspects of disease onset and progression.

The theory that decreasing the caloric intake can improve neurological function goes back over 20 years [39,40] and more recently emerging data from studies on animals and epidemiological studies has led to the hypothesis that caloric restriction could enhance cognitive function and be beneficial for preventing neurological diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), epilepsy and others.

Several hypotheses on how caloric restriction might be linked to cognitive capability have been postulated and include anti-inflammatory mechanisms, reducing neural oxidative stress or promoting synaptic plasticity. Inducing various neurotrophic/neuroprotective factors [41] and enhancing neurogenesis [42–44] were also considered. However, it is very likely that multiple mechanisms underlie the effect of caloric restriction.

Most of the fundamental work on CR with regards to neurology and cognitive function in rodents is based on research on rats. However disease-specific transgenic mouse models have been widely used, including models for neurodegenerative diseases like AD, PD and HD. In addition, model systems for metabolic diseases have been assessed for deficits in cognitive function. Most, if not all, of these mouse models have also been used in conjunction with high fat diets. In contrast to the high fat diet which has a detrimental effect on the phenotype of some neurological disease models (i.e. notably models of AD, as described in the previous section), CR has repeatedly been shown to significantly reduce the neurological defects in some of these disease mouse models. However data from different sources has to be analysed carefully, since there are claims that the beneficial effect of CR is dependent on the metabolic state of the animal and only if there is an imbalance between energy expenditure and energy intake can CR then increase life-span [45]. Furthermore it has been reported that in some cases CR did change behaviour but not cognitive function, which could lead to dissimilar interpretation [46].

Recent research has provided evidence that CR can alter the neuropathology in transgenic mouse models for AD. In Tg2576 animals, a mouse model that replicates certain aspects of the

pathology of AD, including amyloidosis, CR can lead to a down-regulation in the production of amyloid possibly via an activation of ADAM10, a metalloprotease with α-secretase activity [47]. Two other AD mouse models with double mutations in the Amyloid precursor protein (APP; APP*swe*/*ind* (J20)) and Presenilin 1 (PS1; APP*swe*+PS1*M*146*L*), both risk factors for AD, exhibit an early accumulation of amyloid. In these animals the amyloid load in the cortex and the amount of glial activation, a marker of inflammation, was reduced by CR [48]. PS1 and PS2 double ko animals, another model of relevance to AD, show brain atrophy, tau hyperphosphorylation, synaptic dysfunction and cognitive deficits, all hallmarks of AD. In these animals, long term CR not only significantly reduced the tau hyperphosphorylation, apoptosis and neuroinflammation but also reduced the cognitive deficits [49]. A triple transgenic mouse model, in which overexpressing human cDNAs of APP, PS1 and tau are mutated, exhibits age-dependent amyloid accumulation and tau phosphorylation and cognitive deficits in spatial learning tasks. CR and intermitted fasting (IF), a diet in which animals are food deprived every other day, can improve the cognitive function, but only following CR was there a significant decrease of amyloid load and tau phosphorylation [50]. This set of data provides evidence that CR can reduce some of the hallmarks of AD in different animal models and could be beneficial in the disease.

In a mouse model for PD, in which dopaminergic neurons are depleted by treatment with MPTP, CR improved motor function and resulted in neuroprotection. Animals fed with a CR diet performed significantly better on the rotarod, a test for motor function, compared to the animals on AL diet. Pathological analysis of the brains of animals fed on a CR diet revealed an increased number of neurons positive for tyrosine hydrolase (TH), a marker for dopaminergic neurons, suggesting a putative neuroprotective effect of CR. Interestingly, similar results can be achieved by feeding with 2-deoxyglucose (2-DG), a non-metabolizable form of glucose that effectively reduces glucose metabolism. How this neuroprotection is achieved is still not fully understood, however results from dopaminergic cell cultures treated with 2-DG suggest a possible mechanism via a reduction of oxidative stress and preservation of mitochondrial function. [51]. A study that applied short-term CR after the MPTP treatment in mice suggests a modulation of the glutamate homeostasis in the striatum as a basis of the neuroprotective effect [52]. Similar effects of CR on neuroprotection were reported in a primate study, in which monkeys fed on CR diet for 6 months received MPTP and were analysed over 16–18 weeks. Behavioural analysis combined with positron emission tomography (PET) and pathological analysis of the brain led to the conclusion that a beneficial effect of CR on behaviour and neuroprotection was mediated through up regulation of neurotrophic factors [53].

There are several reports that show beneficial effects of CR in a variety of other neurological diseases. For example, fasting has been described as an anti-seizure therapy for many years [54] and CR was shown to be beneficial in a mouse model of epilepsy. EL mice, a genetic model of multifactorial idiopathic epilepsy, present EEG abnormalities and develop secondary generalized tonic–clonic convulsions. CR diet leads to a delay in onset of seizures for several weeks, which correlates to blood glucose levels [55,56]. Additional evidence for CR improving or reversing the disease phenotype has been provided from research in Sandhoff's disease (SD). SD is a neurodegenerative disease caused by a defective Hexosamidase B gene resulting in a glycosphingolipid storage disorder. There is evidence that the neurodegeneration in SD is caused by inflammatory effects like microglial activation, macrophage filtration and oxidative damage which leads to motor dysfunction. Hexosamidase B knock-out mice, an animal model for SD show develop similar pathology and symptoms. In response to CR these animals exhibited significantly improved rotarod performance and increased longevity compared to KO animals on a normal diet [57]. In summary there is increasing evidence of the beneficial effects of CR in a variety of mouse models of neurological dysfunction.

There are reports that take a more careful approach of evaluating the data of CR. However it is important to note that, when analysing the effect of calorie restriction, short-term and long-term deprivation have to be distinguished. Both can lead to an overall increase in activity, due to an increased drive and therefore lead to a positive readout in some cognition paradigms. But only chronic CR leads to a sustained positive effect on cognition [58].

How the described pro-cognitive effects induced by CR are mediated is still to be fully discovered, but recent evidence suggests a modulation of long term potentiation and reduced cytotoxicity in the hippocampus of rats [59–61]. Recent gene expression studies using microarrays reveal significant gene changes in the brain of aging mice indicative of activation of pathways involved in inflammatory response, oxidative stress and neurotrophic support and attenuation of these in mice fed with CR diet [62]. In a study that analysed the gene expression changes induced by CR at various ages in the hypothalamus, it has been shown that CR induced changes genes occur in an age-dependent manner. Major pathways modulated were those involved in brain development and neurogenesis, inflammation, apoptosis and stress responses. Highlighted was the TOR pathway which is involved in nutrient sensing and has been shown to affect lifespan via interaction with the Insulin/IGF pathway [63,64].

Another target activated in CR that has been shown to interact with the Insulin/IGF pathway is SIRT1. SIRT1, the mammalian gene product of the sir2 gene, is a NAD+ dependent deacetlyase that has been described as a critical mediator of the effects of CR in mammalian cells [65] and has been shown to be able to mediate longevity [66]. Transgenic mice with a brain specific knock-out of SIRT1 exhibit a reduction of the beneficial responses to CR[67], whereas animals over-expressing SIRT1 show some metabolic similarities to animals on CR [68]. A transgenic mouse model that allows inducible overexpression of p25, a toxic coactivator of cyclin-dependent kinase 5, display massive degeneration of forebrain with features of AD [69,70]. Resveratrol, a polyphenolic SIRT1 activating compound, injected into the brains of animals 2 weeks after induction of p25 over-expression was able to prevent the neurodegeneration in the hippocampus and the impaired associative learning capability of these animals. Several mechanisms by which SIRT1 promotes this beneficial effect have been described. The tumor suppressor gene p53 that is important in mediating cell death is deacetylated by SIRT1 rendering it unstable and reducing its expression level suggesting this molecular target of SIRT1 could explain the neuroprotective effect [71]. Other reports provide evidence that SIRT1 activation is directly involved in lowering amyloid by activating α-secretase via suppression of ROCK1 [72].

4. Conclusion

Compelling evidence from mouse models has significantly supported clinical and epidemiological evidence for a strong association between dietary risk factors, insulin resistance and neurological disorders such as AD. Importantly these models have identified targets and overlapping pathways that may offer future points of therapeutic intervention. Moreover, the converse concept of calorific restriction has also been effectively modeled in mice offering potential longevity, cognitive remediation and reductions in pathological markers of disease, via potential improvements in insulin sensitivity and metabolic homeostasis. Future studies employing normal and transgenic mice will be essential to confirm the complex interactions played between a variety of susceptibility genes and environmental triggers on disease progression and importantly will help to identify and validate novel therapeutic agents for disease prevention.

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