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Effects of dietary restriction on metabolic and cognitive health

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Abstract

Life expectancy in most developed countries has been rising over the last century. In the UK alone, there are around 12 million people over 65 years old and centenarians have increased by 85% in the past 15 years. As a result of our ageing population, which is due mainly to improvements in medical treatments, public health, improved housing and lifestyle choices, there is an associated increase in prevalence of pathological conditions, such as metabolic disorders, type 2 diabetes (T2D), cardiovascular and neurodegenerative diseases, many types of cancer and others. Statistics suggest that nearly 54% of elderly people in the UK live with at least two chronic conditions, revealing the urgency for identifying interventions that can prevent and/or treat such disorders. Non-pharmacological, dietary interventions such as caloric restriction (CR) and methionine restriction (MR) have revealed promising outcomes in increasing longevity and preventing and/or reversing the development of ageing-associated disorders. In this review, we discuss the evidence and mechanisms that are involved in these processes. FGF21 and H_2S are important molecules involved in the effects of CR and MR in the extension of life span. Their role is also associated with the prevention of metabolic and cognitive disorders, highlighting these interventions as promising modulators for improvement of health span.

Introduction

Life expectancy in most developed countries has been rising over the last century. Data from the Human Mortality Database suggest that children born during the 2000s will reach 100 years of age if the present life expectancy rate remains.(1) In the UK, there are around 12 million people over 65 years old and centenarians have increased by 85% in the past 15 years.(2) The population of developed countries is ageing as a result of the discovery of new drugs and treatments, improvements in public health, low fertility rates,

and changes in the lifestyle of the population.[3] However, ageing is associated with the prevalence of pathological conditions, such as neurodegenerative disease,[4,5] type 2 diabetes (T2D),[6] cardiovascular diseases,[7,8,9] many types of cancer,[10] and others. Statistics show that nearly 54% of elderly people in the UK live with at least two chronic conditions, referred to as multi-morbidity,[11] hence the urgency of identifying interventions that can prevent/treat such disorders and eventually promote the health span extension.

Several lifestyle modifications have been the focus of study as an approach to delay the onset of chronic diseases and the ageing process. Dietary interventions such as caloric restriction (CR) and more specifically, methionine restriction (MR), show promising outcomes in increasing longevity. This improvement is associated with the prevention of ageing-associated disorders and cognitive decline. Thus, understanding the mechanisms involved in life span regulation, as well as control of the health span, with the prevention of development and progression of ageing-related diseases, is of utmost importance if we are to live longer lives.

Sulfur-containing amino acids (SAA) and methionine metabolism

Amino acids that contain the element sulfur in its chemical structure are called sulfur-containing amino acids (SAA). Methionine, cysteine, homocysteine, and taurine are the four amino acids included in this class, being the first two considered the main SAA because they are incorporated into proteins. They are known to play a significant role in protein synthesis, structure, and function.[12] Both methionine and cysteine are abundant in dietary protein sources, although only methionine is classified as an essential amino acid. However, cysteine can be endogenously produced by methionine and serine in the liver and other tissues.[13] The nitrogen balance in adults and the growth rate during childhood are parameters considered for the SAA nutritional requirements. In a study with rodents fed with cereals (low protein diet), the animals restored nitrogen balance and lost body weight with the diet only after methionine and threonine supplementation, suggesting that both are the most rate-limiting amino acids at maintenance of body nutrition.[14]

Methionine is an essential amino acid necessary for protein synthesis in prokaryotic and eukaryotic cells; it also plays a major role as an endogenous antioxidant and is

involved in several physiological and biochemical processes.[15] The methionine metabolism is responsible for the production of essential substances in many physiological pathways. The methionine cycle is the first step of methionine metabolism and includes the biosynthesis of S-adenosylmethionine (SAM) from methionine and ATP by the methionine adenosyltransferase (MAT) (Figure 1). SAM is a key intermediate in methionine metabolism and has many chemical roles. In mammals, the main function of SAM is to serve as a methyl donor in methyltransferase reactions.[16] In the methionine cycle, SAM donates its methyl group to an acceptor metabolite, generating S-adenosylhomocysteine (SAH) catalysed by methyltransferases (MTs). This product is converted to homocysteine by reversible hydrolysis. This sequence of reactions is known as transmethylation and is present in every cell.

Reviewed literature evidences from the last 20 years showed that high plasma levels of homocysteine is a risk factor for the development of neurodegenerative diseases in elderly people, and can be considered a biomarker for the Alzheimer's disease and dementia.[17] Also, hyperhomocysteine is associated with vascular disease and neurotoxicity.[18] Once formed, homocysteine can be remethylated into methionine by methionine synthase (MS) or by betaine homocysteine methyltransferase (BHMT), completing the methionine cycle. MS uses 5-methyltetrahydrofolate (vitamin B12) as a co-factor for the donation of a methyl group, and BHMT requires betaine as the methyl donor.[19] Endogenous methionine formation by MS occurs in most of cells, otherwise, its synthesis using betaine occurs mainly in the liver and kidney [20] (Figure 1).

Homocysteine can also be processed to cysteine via the transsulfuration pathway (TSP). The cystathionine β-synthase (CBS) is the first enzyme in the TSP and is responsible for cystathionine synthesis from the condensation of homocysteine and serine. The second key enzyme in this process is the cystathionine γ-lyase (CGL). This enzyme is responsible for the hydrolysis of cystathionine to cysteine. Furthermore, cysteine can be involved in the synthesis of proteins, glutathione (GSH) and taurine (Figure 1). The TSP and the full conversion of methionine to cysteine is an irreversible process and only occurs in a few tissues: liver, kidney, intestine, and pancreas.[12] Cysteine is considered the rate-limiting substrate for the synthesis of the antioxidant

GSH, which can act as a storage of cysteine and be broken down to favour cysteine formation when its levels are low in the cell.[21]

The TSP is also responsible for production of hydrogen sulfide (H_2S) from the catabolism of cysteine and homocysteine [19] (Figure 2). H_2S is a gas that was classified as toxic for many years. However, more recently, H_2S has been considered as a potential therapeutic agent due to its role as a vasodilator, antioxidant molecule, anti-inflammatory, and insulin release modulator.[22] Additionally, H_2S provided by the TSP has been shown to be an essential molecule for the dietary restriction benefits, such as stress resistance and longevity. [23]

The bioavailability of methionine in the organism regulates the rate of the methionine cycle, to maintain adequate levels of this amino acid in the tissues. The low consumption of proteins or SAA alters the activity of enzymes involved in the TSP, allowing for methionine to be preserved via protein degradation. Furthermore, the concentration of SAM and homocysteine regulates the methionine flux in its metabolic pathways.[21]

Dietary restriction

Dietary interventions have been used for decades as an approach to delay ageing and the development of diseases related to cell senescence. One of the most studied forms of delaying the onset of age-related diseases is by dietary restriction (DR), which includes different nutritional interventions that can bring health benefits in a variety of species.[24,25] Studies have shown that the extension of lifespan is associated with DR in many organisms, including yeast, *C. elegans*, *D. melanogaster*, and rodents. In mammals, different dietary regimens have been associated with health benefits, including intermittent fasting, a decrease in protein intake, or reduction in daily food consumption. These interventions share some similar beneficial features, such as reduced adiposity, improved insulin sensitivity, and glucose homeostasis. However, it is important to note that differences exist between these different approaches and each one has its singularity. In rodents, longevity is mainly attributed to a delay in ageing-related processes, associated with lower incidence of the development of ageing-related diseases and neurodegeneration.[26] A reduction in the activity of nutrient-sensing signalling is possibly one of the main pathways by which DR can increase lifespan.[27,28,29]

One of the most investigated DR interventions is the caloric restriction (CR), [30,31,32] which is defined as a reduction of 20 - 40% of daily food intake with meal frequency being maintained, showing improvements in life and health span.[33] For many years, studies with rodents and primates have been providing evidence that the reduction of daily caloric intake up to 40% without malnutrition improves insulin resistance and prevents the development of several metabolic disorders associated with ageing, as type 2 diabetes (T2D), hypertension, obesity, chronic inflammation and cancer.[34,35,36,37,38] CR diet is also associated with an overall decrease in mortality-related processes in primates.[39] Furthermore, moderate CR with a decrease of only 10% of calorie intake per day was associated with protection against diabetes and decrease in intrahepatic lipid content in a rodent models of obesity. [40]

Clinical trials have been implemented during the years to assess the effects of CR on human health. Some of these studies revealed that CR in adult men and women improves glucose and insulin tolerance, as well as reduces the risk of T2D and cardiovascular diseases.[41] However, the calorie intake and the levels of body fat mass that are associated with the health benefits and any possibility of an increase in the life span in humans is still to be determined. Furthermore, it is important to point out that excessive CR may be accompanied by malnutrition and brings harmful effects to the individuals' health.[42] Studies performed in obese children who were on a low-carbohydrate or a low-fat diet for 2 months, suggested improvements in their body weight and lipid profiles. This effect was associated with low triglyceride serum levels, revealing that DR can improve metabolic parameters in obesity.[43] Additionally, a randomized, controlled clinical study was performed that assessed the effects of CR in non-obese adults, and revealed a significant weight loss accompanied with a decrease in systemic oxidative stress and ageing biomarkers, even 2 years after the dietary intervention.[44]

For decades, the effects of CR in the ageing brain and the development of neurodegenerative diseases have been a topic of intense study. Longer-term clinical trials with CR (4 and 5 years) suggest that a decrease in caloric intake over several years can decrease neuronal damage and delay the onset of symptoms related to Alzheimer's disease (AD) and Parkinson's disease (PD) in elderly individuals.[45,46] In agreement, studies examining neurodegeneration-associated behaviours and dietary interventions,

demonstrated that CR improved locomotor activity in aged rodents compared with mice fed an *ad libitum* diet.[47] In the same approach, CR rats did not exhibit a decline in locomotor activity associated with the ageing process, as reported in animals with free access to food.[48] In addition, mice were submitted to a long-term reduction in calorie intake (during their entire life) preventing the animals against a decline in learning due to ageing, which raises the possibility that it may also protect rodents against neurodegeneration associated with AD mutations. Indeed, a decrease in dopaminergic neuron death was observed in animal models of PD following a 3-months CR regimen.[49,50,51]

Methionine restriction

The primary way of modulating the rate of the TSP is by altering the dietary consumption of methionine. Dietary methionine restriction (MR) is considered a dietary intervention that mimics DR, without CR. Dietary MR can alter enzymatic activity in the methionine cycle and consequently, the synthesis of its metabolites. This nutritional intervention is widely associated with the benefits observed in DR but without malnutrition; reducing adiposity but at the same time increasing both, food intake and energy expenditure.[52]

One of the earliest pieces of evidence that MR could increase longevity in rodents was demonstrated by Orentreich and colleagues (1993). In this study, a reduction of the SAA methionine from 0.86% to 0.17% was able to extend the life span in rodents around 30%, despite the higher food intake promoted by the diet.[53] In another study, control pair-fed animals, consuming the same amount of food as rats on MR diet, did not exhibit an extension of life span, promoting the idea that methionine itself is the key player behind lifespan extension and not necessarily the alteration in total calories consumed. Moreover, blood levels of GSH, a well-known antioxidant molecule, were maintained during ageing in animals on MR diet, and different rodents strains submitted to this dietary intervention revealed a slowing in the ageing process, suggesting that MR may modify the rate of ageing[54] without alterations in reactive oxygen species. Furthermore, studies with *C.elegans* and rodents have shown that the deletion of antioxidant enzymes, e.g. superoxide dismutase (SOD) and gluthathione peroxidase 1

(GPX1), did not alter animal lifespan and was not crucial for the ageing process,[55,56] confirming a separate role for MR in longevity.

The effects of dietary MR in mice were reported by Miller and colleagues,[57] who presented evidence that MR diet is capable of increasing longevity alongside lower hepatic oxidative stress. These mice exhibited low serum levels of insulin, insulin-like growth factor 1 (IGF-1), glucose, and thyroid hormones after a long-life MR diet intake (from 6 weeks of age until natural death).[57] The modulation of rodents' metabolism by the decrease in methionine intake was supported by the observation that rats fed MR diet for 80 weeks had higher insulin sensitivity and lower visceral fat content than animals fed control chow diet.[58] *In vitro* studies revealed that the decrease in adiposity observed in MR-fed rodents was due to a disruption of lipogenesis and lipolysis cycle, with a high rate of both, lipid catabolism and lipid synthesis.[59]

A clinical trial including 26 adults (6 male and 20 female) with metabolic syndrome reported that individuals provided with the MR diet for 16 weeks, or a control diet, decreased body weight and fasting glycemia, irrespective of the diet. Interestingly however, a specific effect only observed in the MR group of volunteers was a decrease in the intrahepatic lipid content and increased fatty acid oxidation. However, this study presented elevated levels of non-compliance in human participants due to poor palatability of the diet. In order to achieve better responses in humans during clinical trials, it is necessary to develop more palatable tasting food in which methionine is selectively decreased. [60]

To understand the physiological mechanisms triggered by dietary MR, a hyperinsulinemic-euglycemic clamp was performed in mice after MR treatment. The mice exhibited a decrease in hepatic gluconeogenesis, followed by higher insulin sensitivity in the liver and high serum levels of the fibroblast growth factor 1 (FGF21), providing evidence of a direct effect of methionine in liver metabolism and FGF21 availability.[61] Increased levels of FGF21 are associated with positive metabolic outcomes, as it has been shown to reduce insulin resistance and hepatic lipids levels in obese and diabetic mice.[62,63] FGF21 is a growth factor released mainly in response to fasting by the liver, being shown to regulate important metabolic pathways.[64] In humans, FGF21 is highly expressed after 7 days of fasting and regulates the energy

balance during this period by adapting metabolic signalling to the reduction of nutrients.[65]

Furthermore, MR was able to decrease lipogenic genes in the liver of aged mice and increase insulin sensitivity in white adipose tissue (WAT) and skeletal muscle. Alongside these findings, aged mice had higher serum and hepatic levels of FGF21, associated with lower circulated leptin levels after 8 weeks of MR. Furthermore, increased FGF21 levels were seen in a short-term 48-hour MR regimen, together with improved whole-body glucose homeostasis. These improvements occurred prior to alterations in animals' body weight/adiposity, adding evidence that MR itself drives the improvements in whole body metabolism. The authors suggested that the MR effects observed were most likely driven by FGF21. [66] Similar increase in FGF21 levels was observed after only 12 hours of MR diet switch in the serum and liver of mice.[61] High FGF21 levels were maintained after 1, 2 and 4 weeks of MR intake.[61] Recently, a clinical trial with overweight and obese women on a low methionine and cysteine diet for one week revealed a significant increase in FGF21 plasma levels. However, the role of each specific amino acid restriction in the modulation of FGF21 content could not be separated, which is a limitation of this study. [67]

Previous work in aged male rats had shown that MR feeding improved oral glucose tolerance maintenance.[58] Our own work compared young (2 month) vs aged mice (12 month) and presented the idea that MR could improve glucose homeostasis after longer (8 weeks) as well as short-term (2 days) restriction, supporting the hypothesis that MR can reverse the age-induced deterioration in glucose and lipid metabolism and handling.[66] These pieces of evidence can be associated with findings that MR increases energy expenditure in young and aged mice together with elevated heat production, which is mainly due to increased brown adipose tissue (BAT) activation and higher uncoupling protein 1 (UCP1) expression in this tissue. [68] Knowing that UCP1 expression is also high in WAT during MR, $Ucp1^{-/-}$ mice were subjected to MR. The findings revealed that the uncoupling respiration in cells is essential for the effects of MR in increasing energy expenditure, but not for improving insulin sensitivity in this tissue. The remodelling of metabolic function in MR animals is integrated with a lower metabolic efficiency as observed with the behaviour of hyperphagia, suggesting the involvement of

a nutrient-sensing mechanism that could compensate for the reduction in methionine by alterations in the body's energy homeostasis. [69] Moreover, the increase in energy expenditure, energy intake, BAT and WAT thermogenesis is abolished in Fgf21$^{-/-}$ mice fed MR diet, which also showed lower insulin sensitivity when compared wild type mice on MR. These data demonstrated that FGF21 is an essential mediator of the MR effects observed in rodents. [70] Additionally, a more recent study, where rats were introduced to MR diet postweaning or at mature age, resulted in different hyperphagia outcomes. In young animals, the hyperphagic effect of MR resulted in an increase in energy intake that overcomes the higher energy expenditure; an effect not observed in ageing rats, indicating that MR could have different outcomes depending on age. [71]

Methionine restriction and obesity

Obesity and diabetes are the major metabolic disorders of public health relevance that have an urgent need for effective interventions. MR promotes loss of body weight and adiposity, increases glucose tolerance, insulin sensitivity, and overall fatty acid oxidation, which makes it a promising lifestyle intervention to tackle these disorders. [57,60,61,66] To investigate if MR could ameliorate obesity, *ob/ob* mice were placed on the diet for 12 weeks; this improved their hepatic lipid profile, with no changes in insulin sensitivity, body weight, and/or adiposity. [72] However, this animal model has an impaired β-adrenergic input, which may correlate with the lack of adipose tissue response to MR. In addition, *ob/ob* mice on MR failed to increase adiponectin serum levels, suggesting a possible role for this hormone in insulin sensitizing effects mediated by MR.[72] Interestingly, the metabolic effects of MR had been investigated previously in the same *ob/ob* mouse model, resulting in an improvement of hepatic steatosis that developed after 14 weeks of treatment. This effect was accompanied by a reduction in hepatic triglycerides levels, a high rate of fatty acid oxidation, and downregulation of inflammatory markers. Insulin levels were also decreased in this study together with increased adiponectin levels.[73] The mechanism by which MR regulates liver metabolism could be related to modulation of micro RNA (miRNA) expression. MR in young and diet-induced obese mice promotes repression and upregulation of several miRNAs that control synthesis and transport of cholesterol, fatty acids, and insulin, suggesting that

that the hepatic benefits of MR in rodents occurs through multiple mechanisms to prevent the accumulation of lipids. [74]

MR diet also appears to improve cardiovascular function in obesity. In diet-induced obese mice, submitted to MR, the dietary intervention led to improved systolic function in middle age (28 weeks old), and was accompanied by a decrease in cardiac inflammation and oxidative stress. [75] This overall improvement in cardiac function was associated with increased levels of H_2S in the heart promoted by the diet (Han, 2020). MR seems to improve cardiovascular function despite the elevated heart: body weight ratio and hyperhomocysteinemia, which are features associated with a high risk of cardiovascular diseases. [75] Ables and colleagues (2015) reported that mice with high plasma levels of homocysteine did not have their cardiac function altered following a MR intake, due to the upregulation of cardioprotective hormones, FGF21 and adiponectin by the diet.[76] Indeed, there is evidence to suggest that high methionine intake could be associated with aortic plaque formation. $APOE^{-/-}$ mice fed methionine supplementation, exhibited high homocysteine levels and increased total aortic lesion area, indicating that methionine levels, and not homocysteine itself, are related to cardiovascular diseases.[77] A recently published clinical trial in North-American (11,567 people) assessed the association between the cardiometabolic disease risk and the content of SAA intake in their diet. The study reported that a high intake of SAA, methionine, and cysteine was closely associated with a cardiovascular disease risk score, high serum cholesterol, glucose, uric acid, insulin, and glycated haemoglobin levels. [78] These findings suggest that low SAA intake, including MR diet, could be a potential intervention to reduce the risk of cardiovascular diseases.

Methionine restriction and diabetes

The development of insulin resistance and T2D have been associated with increased serum levels of methionine and cysteine in many clinical trials, usually before the onset of clinically diagnosed T2D. [79,80,81]. A large cross-sectional study with more than 16,000 individuals showed that the plasma concentration of cysteine was correlated with the body mass index (BMI) and these levels were specifically related to body mass and not lean mass. [80,81] Moreover, metabolite profile studies indicated that alterations in methionine concentration in the plasma may be indicative of insulin resistance and the

risk of T2D. Non-diabetic obese adults had increased circulating levels of methionine if compared with non-obese patients.[79] Also, male patients with T2D show high levels of homocysteine in the blood with lower methionine transmethylation and homocysteine clearance, suggesting an impaired methionine metabolism in this condition. [82] Taken together, these studies propose that changes in metabolism and glucose homeostasis alter SAA metabolism, ultimately resulting in alterations in methionine and cysteine circulating levels.

MR diet has been shown to ameliorate glucose tolerance and insulin sensitivity in several experimental models, preventing the development of T2D. Insulin resistance prone C57Bl/6J mice fed a high-fat methionine restricted diet were found to be more glucose tolerant, with increased insulin sensitivity and decreased intra hepatic lipids, in comparison to high-fat control diet animals. This was associated with high levels of FGF21 and adiponectin, and low circulating levels of leptin and IGF-1. [83] Dietary MR was shown to increases overall insulin sensitivity and tissue-specific insulin sensitivity (liver, skeletal muscle, heart and adipose tissue), by an enhanced insulin-dependent protein kinase B (PKB/Akt) phosphorylation.[61] More recently, New Zealand obese (NZO) mice, a model for polygenic obesity and T2D, were fed a high-fat diet on MR for 9 weeks. MR diet prevented the onset of hyperglycemia in NZO mice and increased FGF21 levels, as well as adiponectin and thermogenic genes in WAT. The same study compared both, vegan and vegetarian diet with an omnivore diet in adults, with evidence that a low protein diet increased FGF21 levels in humans. These hormones were also increased after omnivore individuals switched their diet to a vegetarian diet for 4 days, suggesting a short-term metabolic beneficial effect of reducing protein intake.[84]

The improvement in glucose homeostasis and insulin sensitivity due to MR may be related to improved insulin signalling in the tissues and insulin secretion by the pancreas. *In vitro* studies demonstrated that the limitation of methionine concentration in HepG2 cell media promotes higher PKB/Akt phosphorylation, with a similar pattern occurring in skeletal muscle and WAT of mice fed an MR diet.[61] Similar observations were made in the kidneys of mice on MR for 8 weeks. Aged mice on MR had enhanced insulin-stimulated phosphorylation of PKB/Akt and ribosomal protein S6 (S6). MR diet also induced upregulation of *UCP1*, *Srt1*, *FGF21*, *klotho*, and *B-klotho* gene expression,

suggesting resistance or reversal to the ageing process in this tissue.[85] Corroborating these findings, the supplementation of methionine in a low-protein diet eliminated the beneficial effects observed in diabetic kidneys by the reduction of protein intake in diabetic rats. The specific effects of low methionine provided by the low-protein diet were regarding anti-oxidative stress, anti-inflammation, and anti-fibrosis features in the diabetic kidney, possibly via the mechanistic target of rapamycin complex 1 (mTORC1) in this tissue.[86] Investigating further the effects of MR on the insulin signalling pathway, a mouse model of hepatic protein tyrosine phosphatase 1B (PTP1B) knockout was fed with MR for 8 weeks. The results suggested no additional synergetic effect of PTP1B knockout and MR in insulin sensitivity and lipid metabolism, suggesting that the hepatic MR effects are either not mediated by PTP1B pathway or that there is a ceiling level to which either/both interventions can improve glucose homeostasis.[66]

There is currently no evidence that MR can directly modulate insulin secretion by the pancreas. However, H_2S levels may be an insulin-release modulator in pancreatic beta-cells. It was demonstrated that H_2S inhibits insulin secretion stimulated by glucose and decreases the insulin-stimulated glucose uptake by adipocytes.[87] Nonetheless, the administration of a CGL inhibitor can enhance glucose uptake in adipocytes, which suggests that H_2S might be a novel insulin resistance regulator. Also, in diabetic rats, the CGL pathway is enhanced, confirming the H_2S role in insulin sensitivity in adipose tissue.[87] However, the H_2S effect may differ depending on tissue type, as in the liver H_2S has been reported to stimulate gluconeogenesis and glycogenolysis and inhibit glucose catabolism and glycogen storage.[88] In addition, high-fat diet and the development of diabetes stimulate a reduction of CGL and H_2S production in the rat livers.[89,90] Thus, modulation of the TSP and H_2S production by MR might indirectly intervene with insulin secretion and glucose uptake by the tissues.

Recent evidence suggests that the effects of MR in metabolic health and insulin sensitivity may also differ between sexes. A short-term MR dietary regimen (1 week) was introduced in male and female diet-induced obese mice, showing an improvement in glucose tolerance in both sexes, as expected. However, MR was able to increase energy expenditure and induce the FGF21-UCP1 axis only in males.[91] These findings were corroborated by evidence that only male mice had their lean mass preserved after MR,

while the female mice had a preference to maintain their fat mass, suggesting a sexually dimorphic effect of MR in young mice.[92] However, the underlying mechanisms in MR responsiveness related to glucose homeostasis and insulin sensitivity in males vs. females still need to be investigated.

An alternative, pharmacological approach has also been employed to simulate dietary MR. *In vivo* studies with an oral recombinant methioninase (rMETase), which catabolized methionine to α-ketobutyrate and ammonia, has been shown to prevent diet-induced obesity, increase glucose tolerance and decrease fat mass in mice fed a high-fat diet.[93] Hepatic lipids were also reduced in male mice after rMETase treatment, suggesting a role for this intervention in preventing fatty liver and obesity in rodents.[93] However, no clear evidence has been offered regarding the duration of effects caused by this intervention, and what side effects there may be, bringing attention to the need for more studies in this area. It is nevertheless confirmation that decreasing the levels of methionine, either through dietary or pharmacological interventions, may be a promising and achievable way of preventing the onset of diabetes and obesity, and improving overall metabolic health, thus health span.

Methionine restriction and cognitive function

The influence of different dietary intervention and prevention, to improve memory or delay the onset of neurodegenerative diseases, has been a topic of great interest. During ageing, several functional and structural alterations occur in the brain that impair neuroplasticity and memory.[94,95,96] Initial studies demonstrated that CR can enhance spatial memory in rodents, with age-related motor impairment and learning being prevented following CR for 4 months.[97,49] CR has also been associated with improving synaptic activity and stimulation of neuroprotective signalling in the brain.[98,99,100] In a state of CR, the brain can produce more brain-derived neurotrophic factor (BDNF), offering neuroprotection.[99] Experimental evidence revealed previously that CR induced neurogenesis in the dentate gyrus of the hippocampus is associated with higher BDNF expression.[101] Cognitive impairments exacerbated by obesity were attenuated by CR due to higher levels of N-methyl-d-aspartate (NMDA) receptor subunits, essential for long-term potentiation (LTP) and synaptic plasticity in the hippocampus after 10 weeks.[102] However, some studies have demonstrated that CR

could act in increasing neuronal stem cells via NMDA-independent mechanisms, for example via BDNF. Altogether, improvement in the levels of NMDA receptor and synaptophysin levels in the CA3 region of the hippocampus were observed due to CR and associated with better performance in a spatial memory task.[103]

Long-term CR can also improve working spatial memory in mice.[104] However, some studies associated short-term CR, at later stages of life, with modulation of biochemical markers in the brain related to cognitive decline. The neural cell adhesion molecule (NCAM) and the astrocytic marker glial fibrillary acidic protein (GFAP) were significantly elevated in 24 months-old mice after CR.[105] Late-onset short term CR regimen in rodents was also shown to prevent age-related neurodegeneration in the hippocampus and cortex of rats by decreasing oxidative stress in these regions.[106] In addition, only 7 weeks of CR in old mice (17 months old) reversed changes observed in GSH redox state in the cortex, hippocampus, striatum, and cerebellum, preventing loss of function in these areas.[107] These studies suggest that the introduction of CR in older animals may benefit brain health, preventing the tissue from ageing-related damages.

Preservation of neuronal function within the ageing process is correlated with an increase in life span. The effect of CR in the maintenance of brain integrity seems to be associated with an early shift from glucose to ketone bodies' metabolism in ageing mice.[108] These findings were recently confirmed by another study revealing that CR induced high levels of neurotransmitters and neuronal integrity markers in a postprandial response.[109] Moreover, a low glycolysis activation pathway was observed following CR; these effects were not noticed in *ad libitum* mice. This indicates that an essential role for neuroprotection in ageing may be related to early changes in brain metabolism and glucose utilization.[109]

The beneficial effects of CR in the brain have been being investigated in primates and human studies. Analysis with primates exposed to a chronic, moderate CR revealed an overall reduction in the development of ageing-associated diseases and significant preservation of the white matter in different brain regions. However, the authors observed a faster loss of grey matter without affecting cognitive performances.[110] The impact of 40% CR was also evaluated in small primates (*Microcebus murinus*) for 19 days, demonstrating reduced learning performance. No differences in locomotor capability

were detected in the Rotarod tests.[111] In humans, a clinical trial with healthy elderly individuals reported a significant improvement in memory performance after 3 months of CR regime, compared to increased unsaturated fatty acids intake group and *ad libitum* controls.[112] The results were correlated with improved insulin sensitivity and reduced inflammatory markers, supporting corresponding animal studies, and the concept of conserved brain integrity.[112]

The effects of MR on cognitive performance have also been investigated in recent years. Evidence suggests that obesity is not only a risk factor for the development of T2D and cardiovascular diseases, but also has been correlated with the prevalence of AD and cognitive decline.[113] High-fat diet induced obese mice exhibit impaired learning and memory, accompanied by a reduction in H_2S production in the hippocampus, cortex, and plasma.[114] Higher hippocampal inflammation was also observed. However, obese animals fed high-fat and low methionine diet for the same period, improved in all behavioural tasks, alongside decreased brain inflammation and normalization of H_2S levels.[114] Dietary alterations might alter the methionine cycle, producing chronically elevated levels of homocysteine. The increased plasma concentration of homocysteine has been linked with cognitive decline, dementia, and AD,[115] being shown to induce alterations in the hippocampal plasticity and a slow-onset reduction of synaptic transmission, what confirms its possible role in the pathology of neurodegenerative diseases.[116]

Recent work using C57BL/6J mice fed a high-fat diet for 4 weeks, followed by MR diet for 8 weeks, reported that MR protected the animals against overall inflammation and the brain dysfunction by potentially altering the circadian homeostasis of gut microbiota and the brain.[117] Additionally, behavioural tests performed in older mice (12 and 15-month-old) fed MR for 3 months revealed improved performance in spatial memory tasks, associated with less neuronal damage and synapse damage in the hippocampus. FGF21 levels were significantly elevated after MR; furthermore, FGF21 knockdown severely blunted the MR's effects on the ageing brain.[118] These studies suggest that MR may offer promising therapeutic intervention or even prevention of cognitive decline during ageing and in associated disorders, such as AD.

In support of this idea, a dietary protein restriction (PR) that includes reduced intake of methionine, isoleucine, leucine, phenylalanine, threonine, tryptophan, valine and arginine, improved behavioural performance in an AD mouse model. The authors found a decrease in phosphorylated tau protein in the hippocampus of 9-month-old 3XTgAD mice, suggesting that PR may partially protect the brain against age-related pathologies.[119] Additionally, Tg2576 mice placed on a methionine supplementation in the diet, presented higher levels of homocysteine, which was associated with increased Aβ deposition and behavioural impairments.[120] Moreover, chronic treatment with a methionine-enriched diet promoted increased levels of phosphorylated tau and Aβ plaques, as well as higher inflammation and oxidative stress in the hippocampus of healthy mice. Memory impairments were also observed following methionine supplementation, giving rise to a neurotoxic effect of high circulating levels of methionine, however homocysteine levels were not evaluated in this study.[121]

Interestingly, nutritional deficits in B vitamins might lead to hyperhomocysteinemia and the development of AD pathology. High levels of homocysteine was previously demonstrated to have a bi-directional effect on LTP in hippocampal slices of rats exposed acutely to this amino acid, showing an impairment in neuronal communication what might contribute to cognitive decline.[122] Moreover, rats exposed to long-term homocysteine daily injections (14 weeks) showed alterations in synaptic activity and LTP in the hippocampus, together with changes in spatial learning.[123] Furthermore, vitamin B12 deficiency is associated with poor cognition and the onset of AD[124] and was shown to stimulate PS1 and β-site APP cleaving enzyme (BACE) expression, causing more Aβ plaques deposition.[125] Vitamin B12 is associated with the methionine cycle, as mentioned previously, as well as folate and vitamin B6. Folate concentration is also a factor that could be associated with neurodegenerative diseases and neurodevelopmental disorders. Mild-cognitive impairment observed in T2D patients was correlated with low folate and SAM circulating levels.[126] Also, low levels of folate and vitamin B12 in has been widely correlated with women who gave birth to children with spina bifida.[127] These findings support the idea that modulation of the methionine cycle and its components may serve as an important tool to prevent neuronal damage and subsequent neurodegenerative diseases.

Dietary restriction and Alzheimer's disease

Dietary interventions such as CR not only seems to improve cognition and prevent memory loss during the ageing process, but have also been associated with delayed progression of neurodegeneration.[128,129,130,131,132] Due to the rising global number of elderly people, AD is one of the most prevalent diseases of our time, thus far without effective treatment. AD is considered a multi-factorial syndrome, and its causes are still widely debated. Two types of AD are commonly recognized: sporadic and inherited (familial) AD.[133] The sporadic type is the most common form, accounting for > 90% of the cases, and usually leads to the late onset of the disease. Environmental and lifestyle factors contribute to the development of sporadic AD, including diabetes, hypertension, cardiovascular diseases, hypercholesterolemia, hyperhomocysteinemia, smoking, and others. A small number of cases (less than 1%), are causally directly inherited AD.[134,135,136] Usually, this form occurs earlier in life (from around 45 years), and results from mutations in genes for amyloid precursor protein (APP), presenilin 1 (PS1) or presenilin 2 (PS2), often also categorised by a more aggressive disease progression. The early symptoms of AD include memory impairments, mood and sleep disturbances, and anxiety. With the progression of the disease, deterioration of cognitive functions can be clinically diagnosed,[137,138] yet ultimately requires post-mortem confirmation.

End stage AD is characterised by two main pathological marks that include the extracellular deposition of amyloid-β peptide (Aβ) plaques, and the formation of neurofibrillary tangles containing hyperphosphorylated tau protein.[139] Importantly, recent evidence indicates that soluble, non-fibrillar forms of Aβ and Tau play a more significant causal role compared to the final, aggregated species.[140,141] An early study investigating the effects of dietary modifications to ameliorate neurodegeneration associated with AD-linked mutation was published in 1999. The investigators found that DR for 3 months in PS1 knock in mice (which exhibit spatial memory deficits at 6 months of age)[142] resulted in less damage to hippocampal CA1 and CA3 neurons when compared with *ad libitum* fed animals.[143] In the following years, studies using AD transgenic mice revealed that a short-term CR (4 weeks) can reduce Aβ accumulation;[130] a similar pattern was detected in APP/PS1 mutated mice in long-term CR (18 weeks) resulting in a decrease in neuritic plaque deposition.[144] Female Tg2576 mice (carrying a

double APP mutation,[145] also presented a decrease in Aβ plaque formation after 9 months of a CR diet. The authors reported that CR may promote anti-amyloidogenic α-secretase activity and decrease components of the pro-amyloidogenic γ-secretase complex.[131,146] Furthermore, CR improved age-related behavioural deficits in a triple-transgenic rodent model of AD (3xTgAD, overexpressing mutated PS1, APP and Tau).[147] At 17 months of age, 3XTgAD mice on CR diet for 14 months performed better in the water maze task and displayed higher exploratory behaviour than animals on the *ad libitum* diet. Hippocampal levels of Aβ40, Aβ42, and phospho-tau were also decreased after CR.[148] Elderly humans free of dementia were followed for 4 years. Between the individuals who carried the apolipoprotein E (ApoE) e4 allele, those who their daily calorie intake was elevated showed higher risk of AD,[46] supporting the idea that the reduction in caloric intake could improve AD-like symptoms.

Further studies have been conducted to understand the mechanism(s) by which CR may improve memory and cognition in several animal models. C57/BL6J mice, receiving CR diet for 10 months, presented with enhanced learning and memory capacity in the water maze, associated with a decrease in inflammatory and insulin signalling markers and activation of autophagy.[149] Furthermore, modulation of apoptosis seems to be regulated by CR. Ma and colleagues[150] observed a reduction in apoptosis markers in the hippocampus of C57/BL6J mice on 10 months of CR, which was associated with improved memory in behavioural tests.[150] Finally, the same authors reported improvements in hippocampus-dependent spatial learning associated with higher adenosine monophosphate-activated protein kinase (AMPK) and glucose transporter 4 (GLUT4) levels in the hippocampus, suggesting a possible role of AMPK in this process.[151] Another study demonstrated a correlation between neuroprotective effects of CR in PDAPP-J20 mice for 6 weeks with modulation of glial cells and the autophagy processes.[152] Moreover, ApoE-deficient mice on CR exhibited increased post-synaptic (PSD95) -positive neurons and elevated levels of FGF21 in both, plasma and brain, associated with improved performance in the water maze. This evidence suggested that the neuroprotection of CR may also be dependent on FGF21 signalling,[153] similar to evidence presented above for metabolic disorders.

CONCLUSION

Dietary disease prevention and interventions that extend the life span and ameliorate the impact of ageing have received attention in recent years as a method of extending the period free of disease; i.e. the health span. CR (without causing malnutrition and deficiencies) is one of the most studied forms of prevention and/or reversal of age-related disorders. The reduction in caloric intake can improve brain health and may be a good candidate for reducing the risk of dementia, especially in midlife.(154) However, caution is warranted here, as the controversies surrounding underweight and extreme weight changes and dementia remain unresolved.(155)

Ultimately, current evidence suggests that the total amount of calories is not the key parameter responsible for health benefits, but rather the reduction of specific macronutrients in the diet.(156) Even tough CR can decrease body weight/adiposity and increase insulin sensitivity, the underlying mechanism(s) are still not well understood. In addition, long-term CR in humans may not be achievable and cause a range of deficiencies along the way. Therefore, dietary restriction related to specific nutrients, without CR, offers an attractive alternative, achievable in humans.

One such dietary intervention is MR, which can mimic the positive health span effects of CR without the associated reduction in food intake. Decreasing the amount of methionine in the diet has been suggested as a promising strategy to extend longevity, prevent and/or reverse obesity and metabolic disorders, with many of the effects being driven by its ability to induce FGF21 secretion and production. However, palatability of the MR manipulated diets should be improved to gain more compliance from humans. Vegan diets and foods naturally low in methionine such as green leafy vegetables, nuts, fruits and beans, could possibly recapitulate the positive effects of MR on metabolism; however, these may not be appropriate for children, pregnant women or elderly. Positive outcomes of MR were also reported for cognitive processes, thus opening an opportunity of developing MR mimetics for the prevention of AD and other neurodegenerative diseases. To achieve this, further studies are necessary to identify cellular mechanisms, pathways and targets underpinning the neuropathology of the disease and the role of methionine therein.

Figure 1: Methionine cycle and transsulfuration pathway (TSP). Methionine is converted to S - adenosylmethionine (SAM) by the methionine adenosyltransferase (MAT). Methyltransferases (MTs) produce S-adenosylhomocysteine (SAH), which is converted to homocysteine by S-adenosyl-L-homocysteine hydrolase (SAHH). Homocysteine can synthesize methionine by methionine synthase (MS) and vitamin B12 or by betaine homocysteine methyltransferase (BHMT) and betaine. Homocysteine might also enter the TSP and be converted to cystathionine by cystathionine β-synthase (CBS), which can be processed to cysteine by the cystathionine γ-lyase (CGL), both reactions using vitamin B6 as a cofactor. Cysteine can be used to build proteins and in the synthesis of glutathione (GSH) and taurine.

Figure 2: H_2S production. Hydrogen sulfide (H2S) is produced during the methionine metabolism from the catabolism of homocysteine and cysteine by the enzymatic activity of cystathionine β-synthase (CBS), cystathionine γ-lyase (CGL), and 3-mercaptopyruvate sulfurtransferase (MPST) alongside cysteine aminotransferase (CAT). The production of H2S might produce several cellular responses that cause stress resistance, vasodilation, antioxidant reactions, anti-inflammatory responses, and insulin release.

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Conflict of Interests

The authors declare no conflict of interest for this work.

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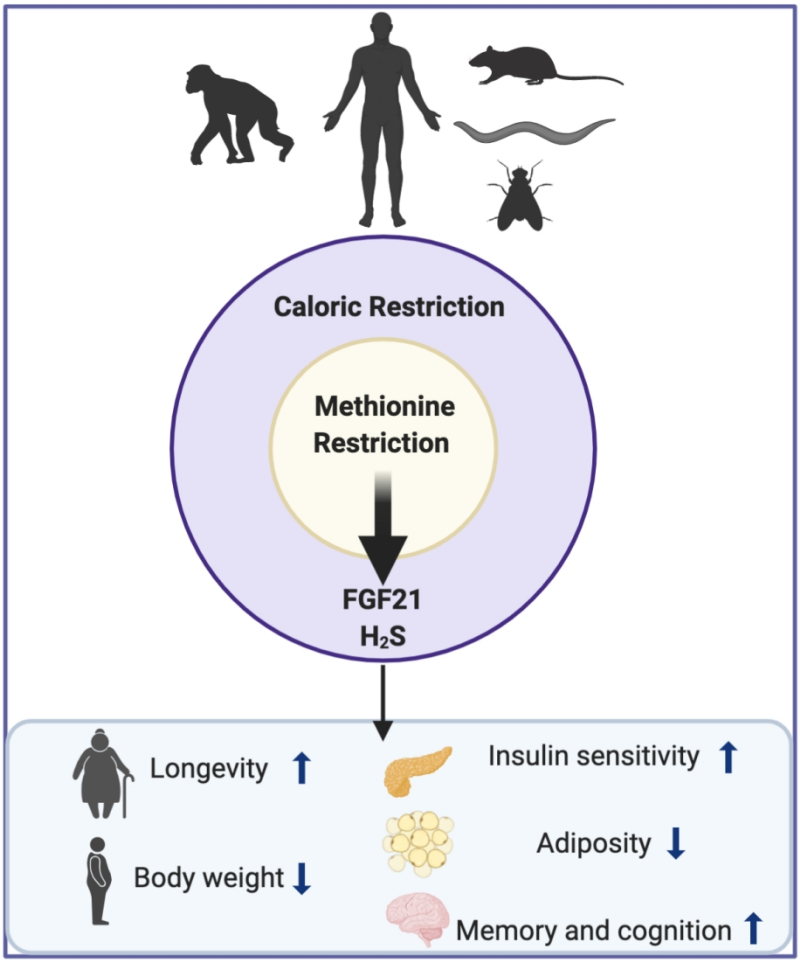

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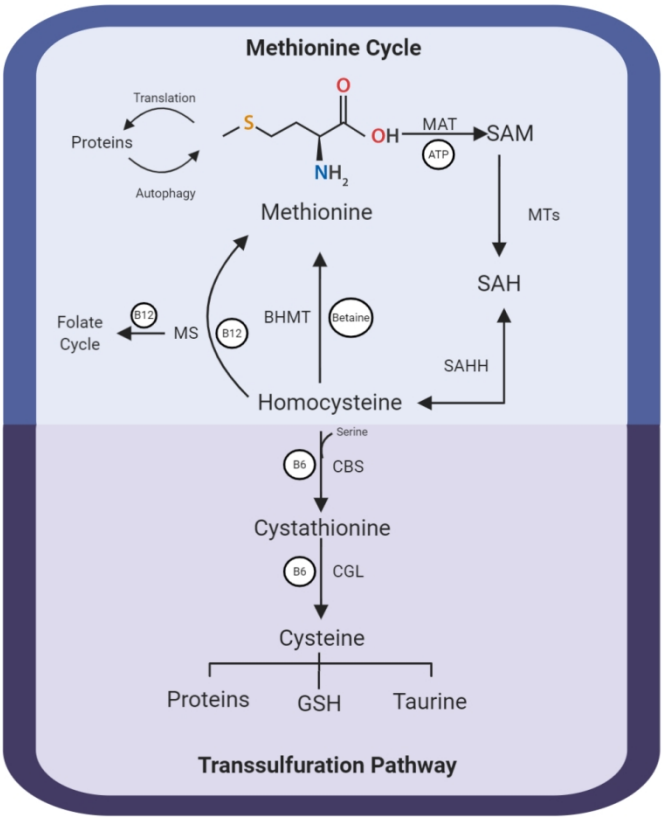

Figure 1: Methionine cycle and transsulfuration pathway (TSP). Methionine is converted to S-adenosylmethionine (SAM) by the methionine adenosyltransferase (MAT). Methyltransferases (MTs) produce S-adenosylhomocysteine (SAH), which is converted to homocysteine by S-adenosyl-L-homocysteine hydrolase (SAHH). Homocysteine can synthesize methionine by methionine synthase (MS) and vitamin B12 or by betaine homocysteine methyltransferase (BHMT) and betaine. Homocysteine might also enter the TSP and be converted to cystathionine by cystathionine β-synthase (CBS), which can be processed to cysteine by the cystathionine γ-lyase (CGL), both reactions using vitamin B6 as a cofactor. Cysteine can be used to build proteins and in the synthesis of glutathione (GSH) and taurine.

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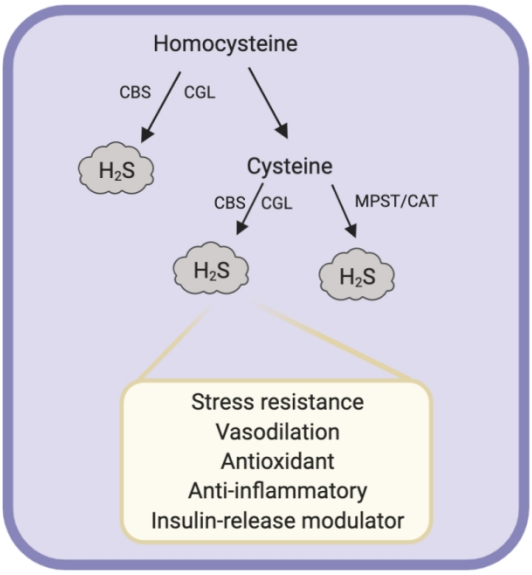

Figure 2: H2S production. Hydrogen sulfide (H2S) is produced during the methionine metabolism from the catabolism of homocysteine and cysteine by the enzymatic activity of cystathionine β-synthase (CBS), cystathionine γ-lyase (CGL), and 3-mercaptopyruvate sulfurtransferase (MPST) alongside cysteine aminotransferase (CAT). The production of H2S might produce several cellular responses that cause stress resistance, vasodilation, antioxidant reactions, anti-inflammatory responses, and insulin release.

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