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Homocysteine and age-associated disorders

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ABSTRACT

There are numerous theories of aging, a process which still seems inevitable. Aging leads to cancer and multi-systemic disorders as well as chronic diseases. Decline in age- associated cellular functions leads to neurodegeneration and cognitive decline that affect the quality of life. Accumulation of damage, mutations, metabolic changes, failure in cellular energy production and clearance of altered proteins over the lifetime, and hyperhomocysteinemia, ultimately result in tissue degeneration. The decline in renal functions, nutritional deficiencies, deregulation of methionine cycle and deficiencies of homocysteine remethylation and transsulfuration cofactors cause elevation of homocysteine with advancing age. Abnormal accumulation of homocysteine is a risk factor of cardiovascular, neurodegenerative and chronic kidney disease. Moreover, approximately 50% of people, aged 65 years and older develop hypertension and are at a high risk of developing cardiovascular insufficiency and incurable neurodegenerative disorders. Increasing evidence suggests inverse relation between cognitive impairment, cerebrovascular and cardiovascular events and renal function. Oxidative stress, inactivation of nitric oxide synthase pathway and mitochondria dysfunction associated with impaired homocysteine metabolism lead to aging tissue degeneration. In this review, we examine impact of high homocysteine levels on changes observed with aging that contribute to development and progression of age associated diseases.

1. Introduction

Development of hyperhomocysteinemia is a characteristic feature of aging. A marked increase in the incidence and prevalence of the disease with advancing age associate with elevated homocysteine levels (Henry et al., 2012). Up-regulation of homocysteine (Hcy) contributes to the development of age-associated disorders, notably bone fractures, poor wound healing, loss of regenerative ability, cardiovascular dysfunction, and decline in renal and cognitive functions. Increased levels of Hcy are seen in 5–7% of the general population (Clarke et al., 1991). The serum level of Hcy increases with age and reaches 16.5±0.5 μmol/l in elderly people of 65 years of age with highest concentrations being found in people 75 years of age or older (Adachi et al., 2002; Rodriguez et al., 2006). The most extreme values are associated with health issues. Some studies have shown the probable association of various endogenous sex hormones and homocysteine levels. It has been shown that the serum level of Hcy is higher in man (11.4±6.1 μmol/l) than in women (9.3±4.5 μmol/l) (Dankner et al., 2004). However, differences are attenuated after menopause (Fonseca et al., 1999).

Elevations in the plasma Hcy concentration in elderly can occur due to impairment of enzymes involved in homocysteine and B vitamins metabolism, impaired metabolism, nutritional deficiencies in vitamin cofactors, lifestyle conditions or other factors including use of drugs (Fig. 1). Decline in renal function due to structural and functional changes that occur in the kidney with aging affects removal of Hcy and causes elevation of Hcy (Glassock and Rule, 2012; Levi et al., 2014; O'Sullivan et al., 2017). Physical inactivity in older age may also play a role in modulating the plasma level of Hcy (Kulkarni and Richard, 2003; Nygard et al., 1995). Numerous drugs can interfere with vitamin cofactors in homocysteine metabolism. Fibrates and nicotinic acid drugs used in the treatment of hypercholesterolemia can raise homocysteine levels of Hcy by approximately 30 percent (Desouza et al., 2002; Rosenson, 2003). Methotrexate and anticonvulsant, such as carbamazepine and valproic acid, impair folate metabolism causing the

Abbreviations: Hcy, homocysteine; HHcy, hyperhomocysteinemia; AD, Alzheimer's disease; CKD, chronic kidney disease; CBS, cystathionine β-synthase; MTR, methionine synthase; MTRR, MTR reductase; MTHFR, methylenetetrahydrofolate reductase; MTRR, 5-methyltetrahydrofolate-homocysteine methyltransferase reductase; BHMT, betaine-homocysteine S-methyltransferase; SAM, S-adenosyl methionine; SAH, S-adenosyl-homocysteine; THF, tetrahydrofolate; NLRP3, nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3; HO-1, heme oxygenase; GFR, glomerular filtration rate; SOD, superoxide dismutase; ROS, reactive oxygen species; NO, nitric oxide; NOS, nitric oxide synthase

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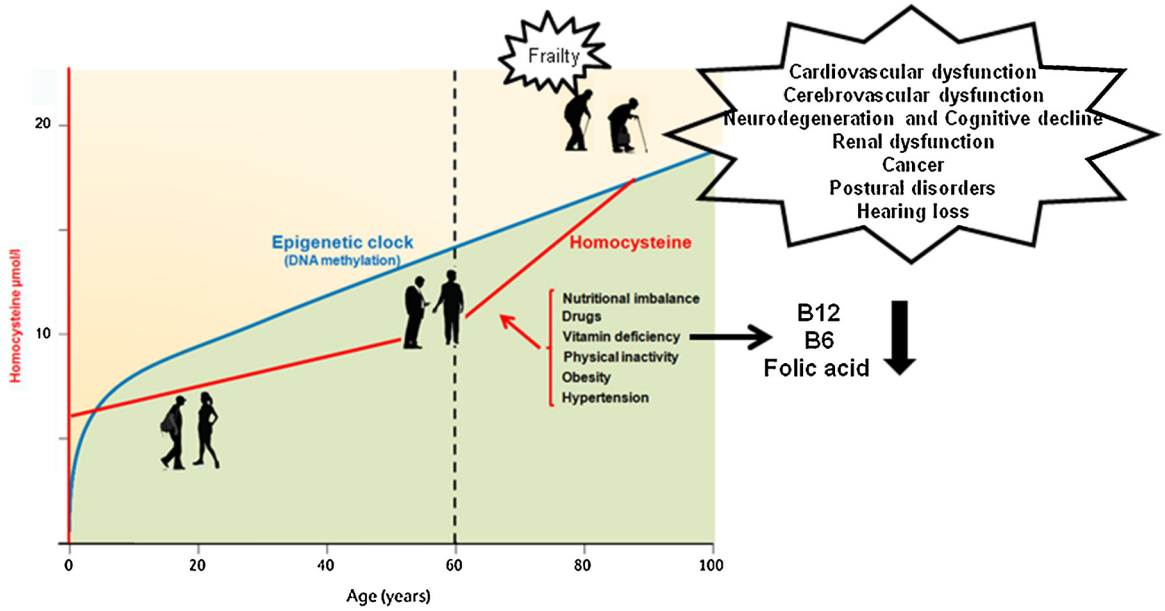

Fig. 1. A schematic diagram relating aging and homocysteine upregulation. Various factors like hypertension, obesity, diabetes, diet and life style cause deregulation of homocysteine level.

rise of Hcy level (Refsum and Ueland, 1990; Schwaninger et al., 1999). Smoking, alcohol consumption and nutritional deficiencies of B vitamins and folate are associated with elevated Hcy in older age (Jacques et al., 2001; Nygard et al., 1998). Most vegetarians develop hyperhomocysteinemia and vitamin B12 deficiency since the major food source of vitamin B12 is meat (Obersby et al., 2013). High Hcy with low vitamin B12 and folate status was found in all centenarians (Malaguarnera et al., 2004; Ravaglia et al., 2000). It has been suggested that centenarians may have some protective mechanisms that allow for their longevity despite elevated levels of Hcy.

DNA methylation has become a hallmark of aging. The age-specific drift in DNA methylation was linked to increased levels of homocysteine and S-adenosylhomocysteine (Kamat et al., 2016; Tapp et al., 2013; Wang et al., 2008). It was reported that regular intake of vitamins involved in the methionine metabolism such as folic acid or vitamin B12 can slow down DNA methylation changes observed during the aging process. Supplementation of vitamins B and D associated with lower homocysteine were shown to slow down the epigenetic drift (Obeid et al., 2018).

The serum level of Hcy associates with increased all-cause mortality risk in a linear fashion. Hyperhomocysteinemia (HHcy) is defined when plasma level exceeds 15 µmol/L (Ravaglia et al., 2006). The level of Hcy reaches the level of 17.8±0.7 µmol/l in patients with heart failure and the level as high as 20.2±1.5 µmol/l in patients with cognitive impairment. The risk of mortality increases for each 5 µmol/L Hcy by 33.6% (Fan et al., 2017). The development of neurodegenerative diseases including Alzheimer's disease (AD) can be directly attributed to neurotoxic effect of Hcy (Eto et al., 2002; Sachdev, 2004; Seshadri et al., 2002; Van Dam and Van Gool, 2009). High Hcy concentrations, over 30 µM, are associated with cognitive impairment (Bonetti et al., 2016; Jin and Brennan, 2008). The prevalence of hyperhomocysteinemia is significantly higher in patients with hypertension and ischemic heart disease (Asfar and Safar, 2007). Chronic hyperhomocysteinemia causes vascular remodeling by instigating vein phenotype in artery thus leading to cerebrovascular and vascular dysfunctions (Basu et al., 2011).

2. Pathways and regulation of homocysteine metabolism

The high level of Hcy results from impairment of Hcy metabolism which lies at the cross-roads of several metabolic pathways. Hcy is the product of the *de novo* pathway of the methionine metabolic reactions catalyzed by S-adenosyl methionine (SAM) and S-adenosylhomocysteine (Dziegelewska et al., 2016). Hcy can be remethylated to methionine via the cobalamin (B12)-dependent and independent pathways or can be metabolized to cysteine and other metabolites via transsulfuration pathway (Finkelstein, 2000). Hcy can also be converted into homocysteine thiolactone by methionyl-tRNA synthetase (MetRS). Metabolism of Hcy depends on function of metabolic enzymes such as methionine synthase (MTR), methylenetetrahydrofolate reductase (MTHFR), cystathionine β-synthase (CBS), 5-methylenetetrahydrofolate-homocysteine methyltransferase reductase (MTRR), betaine-homocysteine S-methyltransferase (BHMT) and availability of cofactors including vitamin B6 and B12 and folate (Fig. 2).

2.1. CBS

Cystathionine β-synthase (CBS) catalyzes pyridoxal phosphate-dependent conversion of Hcy to cystathionine. In animal models, it was shown that during aging the expression of CBS was not changed whereas its activity was significantly decreased (Wang et al., 2017a). The N-nitration of Trp208, Trp43 and Tyr223 and loss of thiolate coordination inhibits the CBS activity and contribute to age-related hyperhomocysteinemia. One of the cause of high level of Hcy is a diet enriched in methionine as confirmed in homozygous and heterozygous CBS knockout mice placed on a high methionine diet (Dayal et al., 2001). Both low dietary folate and cobalamin intake also lead to elevated Hcy since they required for reactions of methionine regeneration. MTR and BHMT catalyze the regeneration of methionine from homocysteine. CBS expression decreases gradually with cellular aging leading to endothelial dysfunction (Albertini et al., 2012).

2.2. MTR, MTRR and MTHFR

For functional activity, MTR requires vitamin B12 (methylcobalamin) and MTR reductase (MTRR). In the absence of functional MTRR, MTR does not convert Hcy into methionine. Methylenetetrahydrofolate reductase (MTHFR) regulates the partitioning of folate-activated one carbon units between the folate-dependent *de novo* thymidylate and Hcy remethylation pathways (Fig. 2). MTHFR converts 5,10-

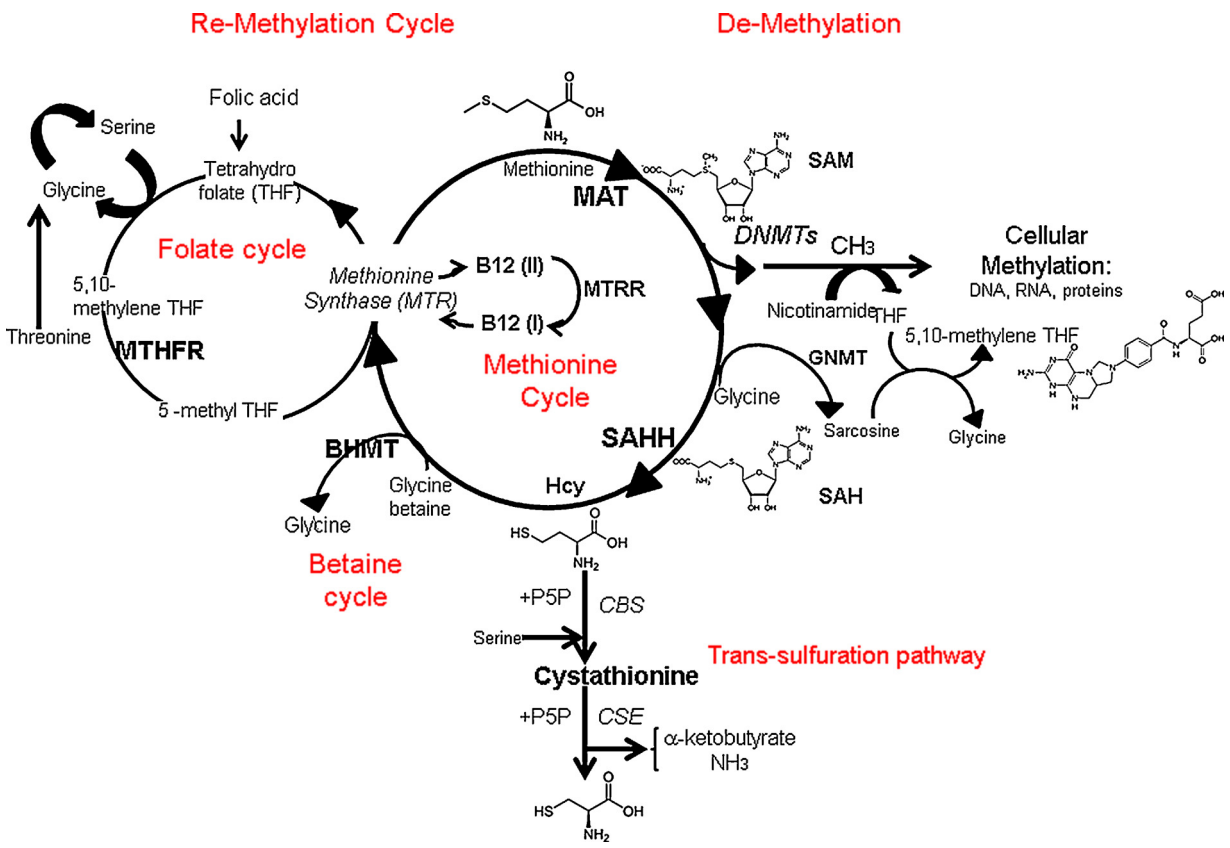

Fig. 2. Intersections of methionine cycle, folate cycle, betaine cycle, transsulfuration pathway and methylation. Methionine is converted to S-adenosylmethionine (SAM) by methionine adenosyltransferase (MAT). SAM serves as a methyl-donor in various methyltransferase reactions. Glycine N-methyltransferase (GNMT) converts SAM to S-adenosylhomocysteine (SAH) generating sarcosine. SAH undergoes reversible hydrolysis by adenosyl-homocysteine hydrolase (SAAH) yielding homocysteine (Hcy). Homocysteine can be remethylated into methionine or converted into cysteine via transsulfuration pathway. In methionine synthase (MTR) reaction, the one-carbon methyl group of methylenetetrahydrofolate (5-methylene THF) is transferred to Hcy to form methionine. The cofactor for this reaction is B12 in the form of methylcobalamin. Betaine-homocysteine S-methyltransferase (BHMT) uses betaine to catalyze the conversion of homocysteine (Hcy) to methionine. The transsulfuration pathway is initiated by cystathionine β-synthase (CBS), which catalyzes conversion of homocysteine into cystathionine. Cystathionine γ-lyase (CSE) then converts cystathionine to cysteine CBS and CSE catalyzed reactions area vitamin B6 -dependent. Pyridoxal 5'-Phosphate (P5P) is the active form of Vitamin B6.

methylenetetrahydrofolate into 5- methylenetetrahydrofolate (5-MTHF), a product required for reaction of remethylation of Hcy and away from thymidine synthesis. 5-methylenetetrahydrofolate (5-MTHF) acts as a substrate with vitamin B12 and S − adenosyl methionine (SAM) serving as cofactors for methionine synthase. Functionality of MTR is maintained by MTRR, which catalyzes the reductive reactivation of inactive MTR bound to oxidized cobalamin to maintain its active form using SAM. Polymorphisms in MTR and MTHFR act independently to elevate Hcy concentrations by compromising different parts of the pathway that might not interact directly with one another (Harmon et al., 1999; Ho et al., 2013). Consistent with central role of MTHFR, the genetic variations of MTHFR that compromise the gene function, lead to occlusive vascular disease, neural tube defects, Alzheimer's disease and other forms of dementia (Efrati et al., 2014; Mansouri et al., 2013). In the population-based Rotterdam Scan Study, polymorphism of folate-related gene MTHFRC^{677}→T was shown to be associated with accumulation of Hcy (de Lau et al., 2010). However, this study did not find relationship between polymorphisms and cognitive performance or severity of cerebral white matter lesions. In another study, C^{677}→T polymorphism in MTHFR was shown to be associated with higher plasma concentrations of Hcy and concomitant risk of brain atrophy and brain volume deficit (Rajagopalan et al., 2012). MTHFR polymorphism is seen in 5–20% of North America and Europe population (Jacques et al., 1996). Mutation of MTHFR results in reduced enzymatic activity and consequently accumulation of Hcy (Rozen, 1996). Plasma concentrations of folate, B12 and 5-MTHF ($p = 0.005$) are reduced in elderly people over 65 years old who had dementia (Bednarska-Makaruk et al., 2016). Although, deficiencies of 5-MTHF or vitamin B12 were not associated with changes in DNA methylation in demented patients as compared to age-matched controls, these changes correlated with the folate levels (Selhub et al., 2007, 2009). Similar to folate, deficit of vitamins B12 and B6 can lead to cognitive deficit (Selhub et al., 2009). High level of Hcy persists in patients with B12 deficiency even in the presence of sufficient level of folate. Only concurrent supplementation of B vitamins and folic acid has been reported to reduce the level of Hcy (Vogel et al., 2009). Knockout studies showed that homozygous mutant mice lacking functional MTFHFR had increased levels of Hcy and reduced levels of SAM and 5-methylene-THF (Chan et al., 2008; Ghandour et al., 2004; Jadavji et al., 2012, 2015). MTHFR deficiency resulted in a significant decrease in levels of DNA methylation and the levels of glutamate and γ-aminobutyric acid (GABA) in cerebellum, hippocampus and thalamus. MTHFR deficiency affected hippocampal functions and caused impairments in cognitive and motor functions.

2.3. BHMT, GNMT and MAT

The alternative remethylation pathway of Hcy utilizes zinc metalloenzyme betaine–homocysteine S-methyltransferase (BHMT). BHMT has a limited tissue distribution; it is highly expressed in the liver and kidney but not in brain suggesting that alternative remethylation pathway is likely absent in the brain (Chen et al., 2010). Methionine

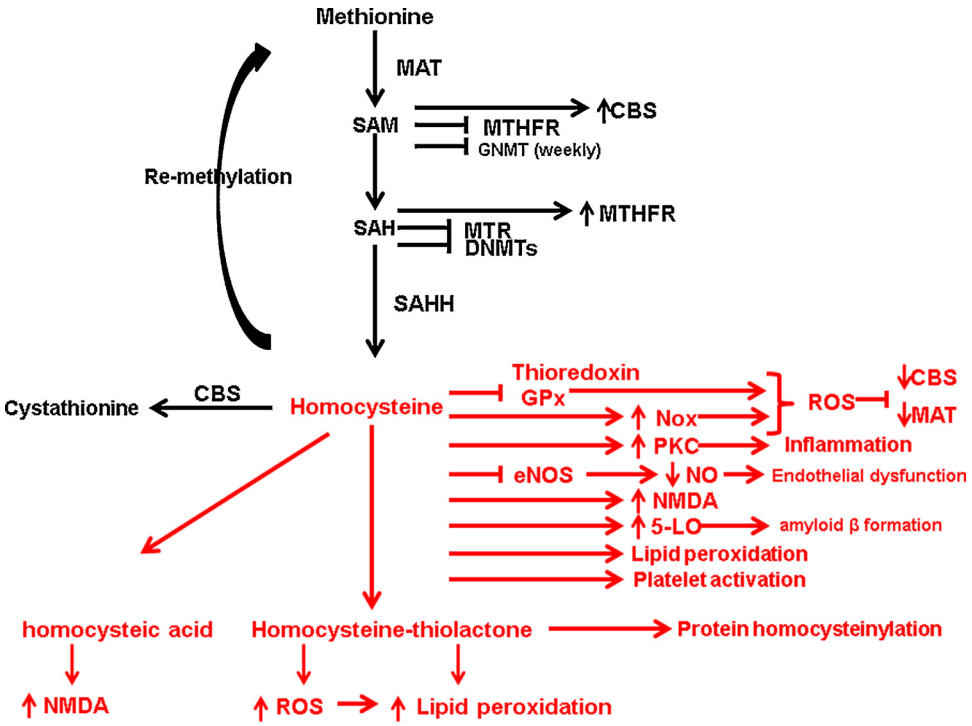

Fig. 3. Putative effects of homocysteine-induced cellular dysfunction. Exposure to homocysteine leads to inactivation of endothelial nitric oxide synthase (eNOS), reduced bioavailability of nitric oxide resulting in impaired endothelium-dependent vasodilator function. As a consequence of homocysteine-mediated inhibition of antioxidant enzymes (glutathione peroxidase (GPx) and thioredoxin) and activation of NOX family of NADPH oxidases, accumulation of oxygen-derived free radicals (oxidative stress) results in lipid peroxidation of membranes, cross-linking of proteins, and fragmentation of DNA. Oxidative stress leads to inactivation of methionine adenosyltransferase (MAT) and cystathionine β-synthase (CBS), thus increasing the intracellular homocysteine concentration. Homocysteine upregulates 5-lipoxygenase (5-LO) that leads to production of leukotrienes and amyloid β formation. Homocysteine causes direct neurotoxicity by activating the N-methyl-D-aspartate (NMDA), subtype of glutamate receptor.

adenosyltransferase (MAT) catalyzes conversion of methionine to SAM using adenosine triphosphate (ATP) as a substrate. MAT is present in three isoforms, MAT1, MAT2 and MAT3 (Sullivan and Hoffman, 1983). MAT2 is present in all tissues and has a high affinity for methionine, whereas MAT1 is present only in the liver. Consistent with expression profile of MAT2 and glycine N-methyltransferase (GNMT), SAM and SAH concentrations were found to be highest in the liver and being lowest in the brain tissue (Chen et al., 2010). MAT contains 10 cysteine residues per subunit and for this reason it is a perfect target for oxidation and nitrosylation the processes that increase with age (Avila et al., 1998). Oxidation of MAT by reactive oxygen species (ROS) and oxidized glutathione or nitrosylation by NO-derived species results in conformational changes leading to rapid and complete inactivation of the enzyme. The metabolic product of the reaction catalyzed by MAT, SAM, acts as activator of CBS converting Hcy into less toxic cystathionine (Finkelstein et al., 1975). However, on the other hand, SAM is alosteric inhibitor of methylenetetrahyrofolate reductase (MTHFR) and BHMT (Fig. 3), thus decreasing availability of substrate for MTR catalyzing reaction of homocysteine remethylation (Corrales et al., 2002; Finkelstein and Martin, 1984; Kutzbach and Stokstad, 1967). In BHMT, zinc atom is coordinated by three cysteines (Cys 217, 299 and 300). Zinc ion is required for proper protein folding. Oxidation of cysteine residues and formation of an intramolecular disulfide-bond between two of these cysteines impairs zinc binding leading to displacement of zinc and consequently BHMT inactivation (Miller et al., 2005). Long-term exposure of BHMT to oxidizing environment causes irreversible loss of its catalytic Zn and a corresponding loss of enzymatic activity and inability of BHMT to convert Hcy to methionine.

Variations in GNMT and ALDH1L1 were shown to associate with high levels of Hcy. The of ischemic stroke correlates with a protein encoded by aldehyde dehydrogenase 1 family member L1 gene (ALDH1L1), which converts 10-formyltetrahydrofolate to tetrahydrofolate (THF) (Williams et al., 2014). GNMT catalyzes the conversion of SAM to SAH, using SAM as the methyl donor. The activity of GNMT is inhibited by 5-methyl THF, synthesis of which is suppressed by SAM. Therefore, folate deficiency and decrease in SAM concentration will activate GNMT. Folate deficiency is relatively common in older adults. GNMT activity also increases with aging (Mays et al., 1973). Age-related activation of GNMT is likely regulatory response to prevent hepatic accumulation of SAM and the development of non-alcoholic fatty liver disease (NAFLD), which is common in the elderly (Gong et al., 2017; Varela-Rey et al., 2010; Yen et al., 2013). Although GNMT activation has clearly been shown to prevent liver steatosis, GNMT mediated depletion of SAM, a methyl group donor, has a negative impact on DNA and certain tRNA methylation. The methylation of tRNA adenosine occurs at different positions (9, 14, 2257 and 58) to form 1-methyladenosine (m^1A) (Oerum et al., 2017). The methylation at adenosine 58 (m^1A58) is vital for tRNA stability. tRNA hypomethylation results in degradation of unmethylated tRNA, accumulation of tRNA fragments, and inefficient and inaccurate proteins synthesis (Nachtergaele and He, 2017). Changes in the rate and accuracy of protein synthesis and protein turnover are among the main molecular characteristics of aging (Gonskikh and Polacek, 2017). Furthermore, tRNA methylation is required for activation stress response pathways that make aging tissue sensitive to stress.

2.4. SAM

SAM plays a pivotal role as methyl donor in various methylation processes. SAM is also important regulator of methionine, folate and choline cycles. SAM inhibits the activity of MTHFR by regulating the availability of 5-methyl-tetrahydrofolate (5-methyl THF) for Hcy remethylation while stimulating CBS activity (Dekou et al., 2001). SAM inhibits MAT2, while MAT1 is less affected by SAM (Kotb and Geller, 1993). GNMT has low affinity for SAM, thereby, SAM can only weekly inhibit GNMT. After donating methyl group SAM converts into SAH. The SAH restores SAM-mediated inactivation of MTHFR but suppresses the activities of both methionine synthase and methyltransferases (Fig. 4). S-adenosyl-L-homocysteine hydrolase (SAH hydrolase or SAHH) catalyzes the reversible hydrolysis of SAH to Hcy and adenosine. Low levels of SAM and high levels of SAH increase the risk of dementia (Obeid et al., 2011). With aging, the SAM concentrations tend to decrease in whole brain, brainstem, and hypothalamus (-25%) while SAH concentrations increase by 90% in striatum and by 160% in cerebellum (Gharib et al., 1982). Suppression of age-dependent SAH accumulation in *Drosophila* flies was shown to increase their life span (Parkhitko et al.,

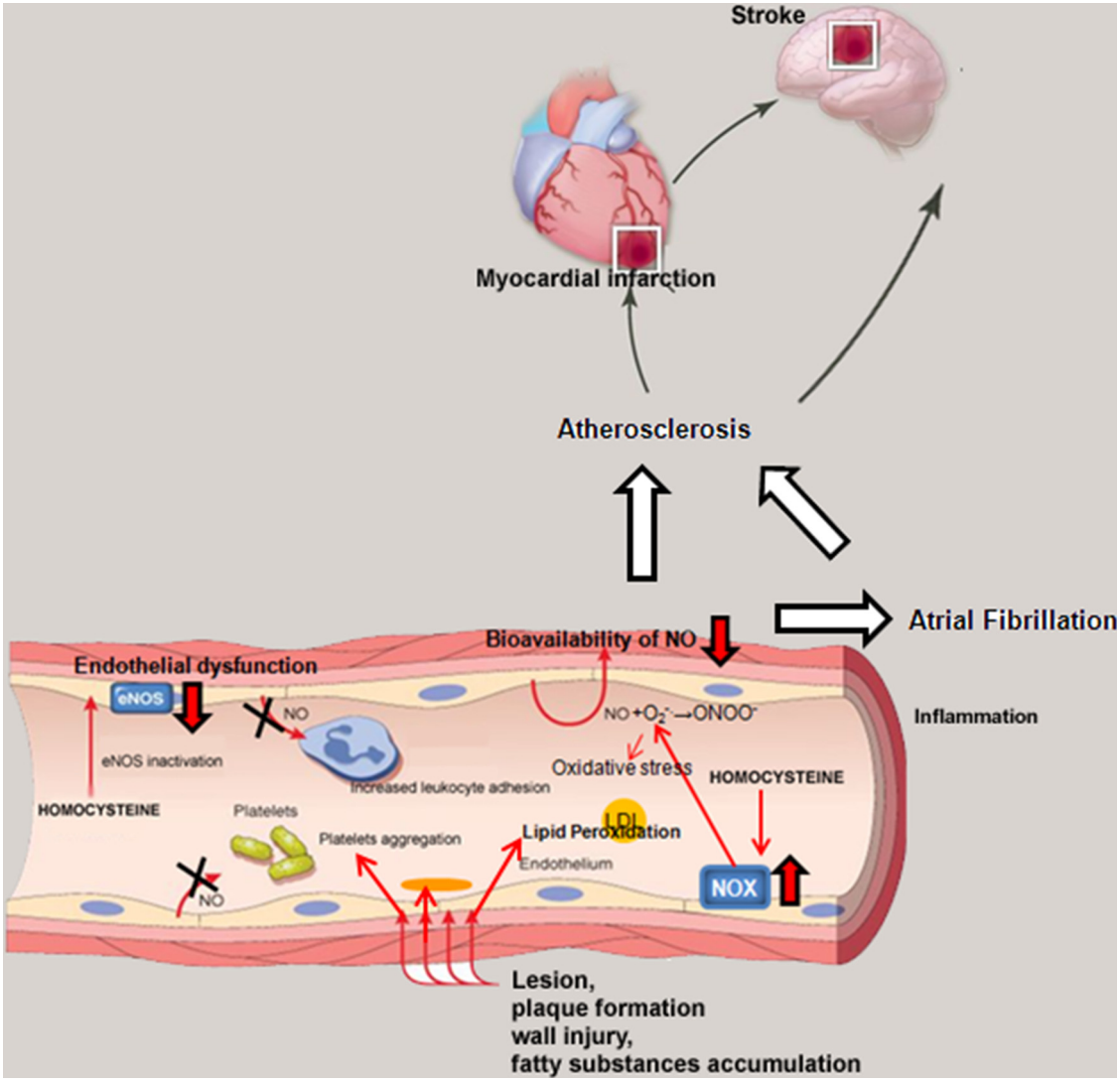

Fig. 4. A simplified scheme illustrating homocysteine induced vascular dysfunction. Exposure of endothelial cells to homocysteine leads to inactivation of endothelial nitric oxide synthase (eNOS), reduced bioavailability of nitric oxide (NO), increased platelet aggregation, oxidative stress and lipid peroxidation. Low-density lipoprotein cholesterol (LDL) is deposited in the endothelium and undergoes oxidative modification, resulting in oxidized LDL that stimulates endothelial cells to express adhesion molecules. Deposition of fibrin and activated platelets on the dysfunctional endothelium catalyzes the plaque formation.

2016). It was shown that accumulation of SAM during ageing of *Drosophila* flies coincided with overexpression of GNMT (Obata and Miura, 2015). Consistent with these results, overexpression of GNMT suppressed SAM accumulation in old flies and extended their longevity. However, remarkable decrease in both SAM and SAH was reported in different tissues in aging rats and mice (Jeon et al., 2018; Stramentinoli et al., 1977). In short-living growth hormone transgenic mice liver SAH and GNMT mRNA levels were suppressed as compared to wild type mice while level of SAM was not (Brown-Borg et al., 2018). The resulting SAM:SAH ratio was higher in transgenic mice.

Knockdown of MAT was shown to shorten lifespan. Long-lived Snell dwarf mice exhibit high expression of MAT and high level of SAM in liver (Vitvitsky et al., 2013). In the long-lived Ames dwarf mice, the methionine flux through the transsulfuration pathway was enhanced at the expense of methionine recycling via remethylation (Uthus and Brown-Borg, 2006). The longest living rodent, naked mole rats (*Heterocephalus glaber*), have very low levels of methionine and cysteine, almost half of what observed in mice. (Ma et al., 2015; McIsaac et al., 2016). The CBS activity is also low in the naked mole rats but it can be activated to a higher degree by SAM as compared to other species (Dziegelewska et al., 2016).

An inverse relation exists between Hcy and NAD(H) levels (Guest et al., 2015). Hyperhomocysteinemia associates with decreased level of SAM and consequently reduced the overall methylation (Li et al., 2017). Depletion of SAM as a methyl donor, in turn, affects nicotinamide (NAM) methylation by nicotinamide N-methyltransferase (NNMT) in NAD^+ salvage pathway thus diminishing the pool of regenerated NAD^+ and overall cellular redox status (Elhassan et al., 2017). The changes in the level of NAD^+ may then influence the activity of various enzymes which are involved in epigenetic control, DNA repair and genomic stability such as histone deacetylases (HDACs) and poly (ADP-ribose) polymerases (PARPs) (Berger and Sassone-Corsi, 2016).

3. Role of homocysteine in multisystem age-related degenerative disorders

3.1. Cardiovascular dysfunction

About 66% of deaths from cardiovascular disease occurs in people age 60–79 years old and reaching 84.7% in men and 85.9% in women aged over 80 years old (American Heart association, Statistical fact sheet 2016 update). It was reported that 5 μM/L increase in the level of

Hcy exceeding 9 μM/L amplifies cardiovascular mortality by 50% and doubles death rate from other causes including respiratory and neurodegenerative diseases (Vollset et al., 2001). Deaths occur in people age 60–79 years old and reaching 84.7% in men and 85.9% in women aged over 80 years old (American Heart association, Statistical fact sheet 2016 update). It was reported that 5 μM/L increase in the level of Hcy exceeding 9 μM/L amplifies cardiovascular mortality by 50% and doubles death rate from other causes including respiratory and neurodegenerative diseases (Vollset et al., 2001). The correlation between hyperhomocysteinemia and atherosclerotic disease was first identified by McCully (McCully, 1969, 2005). The Jackson Heart Study, a longitudinal population-based investigation initiated in 2000, showed positive association between Hcy, age and the risk of cardiovascular disease. Furthermore, HHcy shortened the survival from cardiovascular disease. Homocysteine at the concentration of 10 μmol/L or higher is considered a risk factor in the development of cardiovascular diseases and ischemic heart disease. The elevation of plasma concentrations of homocysteine over 15–16 μM leads to coronary and peripheral artery and venous vessel diseases (Moustapha and Robinson, 1999; Schnyder et al., 2001). The level of Hcy was found to be independent predictors for spontaneous reperfusion in ST segment elevation myocardial infarction (STEMI) assessed by coronary angiography (Li et al., 2018). Several case control studies have pointed towards a correlation between total serum homocysteine and the incidence of coronary, carotid, and peripheral vascular disease (Okura et al., 2014). HHcy was related to aortic mineralization in patients with ischemic heart disease and prevalence of calcific aortic valve disease (Novaro et al., 2004; Pena-Duque et al., 2012). High level of Hcy associates with both the prevalence and incidence of peripheral arterial disease, which is the third leading cause of atherosclerotic cardiovascular morbidity (Amrock and Weitzman, 2016; Krause et al., 2016). Accumulation of Hcy positively associates with lower extremity arterial disease, which is occurring preferentially in elderly persons and indicates generalized atherosclerosis (Bertoia et al., 2014; Kumakura et al., 2015). The Homocysteine and Progression of Atherosclerosis Study (HPAS), which was instituted in 1991 and conducted at Oregon Health Sciences University, showed that 85% of participants had been diagnosed with lower extremity arterial disease (Taylor et al., 1999). The subjects with HHcy were significantly more likely to be men with much lower survival rate. An elevated plasma homocysteine level (> 14 μmol/L) in men and women had influence on the risk of death from cardiovascular disease. Sclerotic stenosis or occlusions of the arteries of the lower extremities presents an increased risk for potentially fatal cardiovascular events. It was reported that 38.9% of patients suffering from lower extremity arterial disease with Hcy level over 15 μM/L died as a result of cardiovascular complications (Jud et al., 2018).

Among common complications after myocardial infarction are atrial fibrillation, hypokinesia of the left ventricle and consequently formation of intra-cardiac thrombi. Strong correlation was shown between elevated level of Hcy and the incidence of vein thrombosis in case-control studies (Cattaneo, 2001; Cattaneo et al., 2001). The possible mechanism was described due to Hcy induced platelet adhesion to endothelial cells, LDL atherogenesis and formation of pro-coagulant red blood cell-derived micro-particles (Xie et al., 2014; Zhang et al., 2014). Few meta-analysis demonstrated a modest or low association between HHcy and vein thrombosis with cut-off levels for HHcy between 1.1 mg/l and 3.4 mg/l (Den Heijer et al., 2005; Lijfering et al., 2007; Naess et al., 2008; Ray, 1998). However, meta-analyses using MEGA 1999-2004case-control study from the Netherlands have shown no association between elevated homocysteine concentrations and risk for vein thrombosis (Ospina-Romero et al., 2018). It is still unclear whether elevated homocysteine concentrations can cause venous thrombosis.

3.1.1. Hypertension

Homocysteine has been positively associated with both diastolic and systolic blood pressure respectively (Lim and Cassano, 2002; Verdoia et al., 2015). The rise in Hcy concentration by 5 μmol/L increased diastolic and systolic blood pressure in men by 0.5 and 0.7 mmHg, respectively (Lim and Cassano, 2002). With advancing age, changes in the level of homocysteine, but not vitamin B12, increased arterial stiffness. It was reported that high plasma homocysteine is independent determinant of aortic augmentation index and arterial stiffness in arterial hypertension (Tayama et al., 2006; Vyssoulis et al., 2010). In people age 65 and older, the strong positive association was found between serum Hcy concentrations and the prevalence of increased arterial stiffness and high carotid resistive index, which is associated with a large difference in flow velocity between the systolic and diastolic phases estimated by carotid ultrasound and arterial stiffness (Chen et al., 2018; Okura et al., 2014; van Dijk et al., 2014). Chinese hypertensive subjects with high level of Hcy (> 15 μmol/l) and low platelet count had shown to have high incident rate of first stroke (Kong et al., 2018).

The animal study demonstrated that sub-chronic hyperhomocysteinemia enhanced the systolic blood pressure after sympathomimetic stimulation while didn't affect normal blood pressure (Miyajima et al., 2015). Severity of HHcy was potentiated by cholesterol uptake. It was suggested that vasoregulation was compromised by Hcy mediated lamellae disruption rather than by induced oxidative stress. Experiments in 10 weeks spontaneously hypertensive rats showed that infusion of homocysteine caused depressed cardiac contractility (Ganguly and Alam, 2015).

In a study based on hospitalized hypertensive patients during the acute phase of a stroke, HHcy was observed in 90.4% of patients (Zhang et al., 2016). The hypertensive patients with atrial fibrillation, which is common cardiac arrhythmia, have higher homocysteine and arterial stiffness as compared to hypertensive patients without atrial fibrillation (Shi et al., 2016). The prevalence of atrial fibrillation increases with age ranging from 0.7% in people aged 55 to 59 years to 17.8% for those ≥85 years of age (Villani et al., 2018). Homocysteine level in hypertension elderly patients with atrial fibrillation increases up to 20.8 ± 4.79 μM/L as compared to 13.8 ± 4.43 μM/L in patients without atrial fibrillation. Elevated homocysteine increases the risk of left atrial appendage thrombus and occurrence of stroke/transient ischemic attack in patients with atrial fibrillation (Yao et al., 2017b). The concentration of Hcy in atrial fibrillation patients with ischemic stroke increased progressively with age and was higher as compared to concentration in elderly people without stroke of the same age (Yao et al., 2017a).

3.1.2. Mechanism of homocysteine-related cardiovascular damage

The primarily mechanisms leading to vasomotor dysfunction are the dysfunction of nitric oxide (NO) pathway and the simultaneously increased thromboxane A2 (TXA2) activity both in vessels and platelets, suppression of endothelium-derived hyperpolarizing factors, activation of angiotensin II receptor-1, induction of endothelin-1, and oxidative stress (Chen et al., 2011; Cheng et al., 2009; Hooshmand et al., 2013). Among the major culprits in Hcy-induced endothelial injury are reactive oxygen species (ROS) and nitrogen species such as peroxynitrite (ONOO-) (Fig. 5) (Fujiki et al., 2012; Mayo et al., 2012; Tsen et al., 2003). On one hand, Hcy suppresses activities of anti-oxidative enzymes such as glutathione peroxidase, superoxide dismutase, thioredoxin and peroxiredoxin (Fig. 4), and on the other hand, it triggers activation of NADPH oxidase (Nox), which is primary source of ROS (Signorello et al., 2009). Hcy also affects NADPH subunit p67phox and Nox2 (Xu et al., 2017). Hcy accumulation increases NADPH oxidase 1 (NOX1) and mitochondrial nitric oxide synthase (mtNOS) activities and concomitantly decreases thioredoxin and peroxiredoxin activities leading to oxidative stress and mitochondrial mitophagy (Tyagi et al., 2011b). HHcy results in accumulation of superoxide and 3-nitrotyrosine and depletion of hydrogen sulfide in the endothelium that cause impairment of endothelium-derived hyperpolarizing factor mediated relaxation of small mesenteric arteries (Chen et al., 2011; Cheng et al., 2018; Tyagi et al., 2011b). Exposure of human umbilical vein

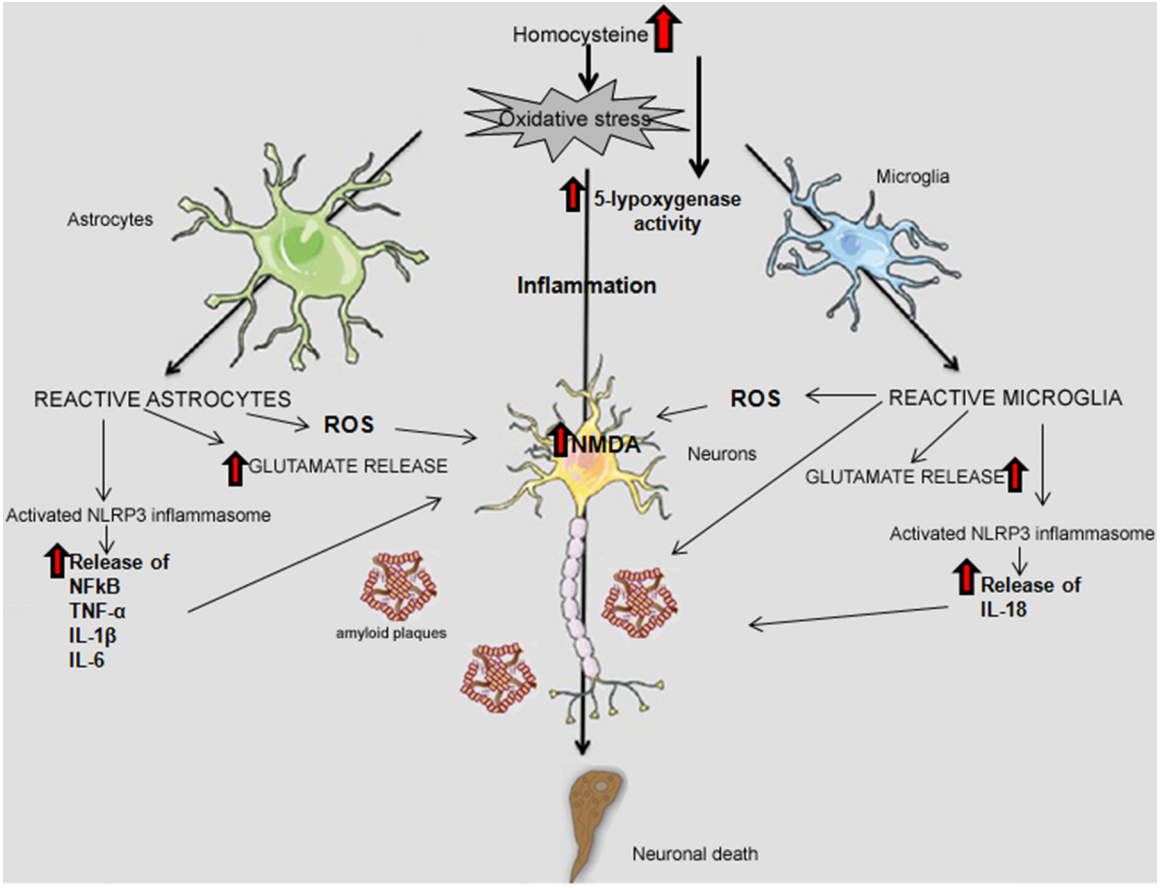

Fig. 5. A simplified scheme illustrating some of the mechanisms underlying Homocysteine induced neuroinflammation and neurodegeneration. Homocysteine promotes activation of microglia and astrocytes resulting in neurotoxicity.

endothelial cells (HUVECs) to Hcy in dose-dependent and time-dependent manner induces an increase in cellular NOX2, p47phox, and NOX4 resulting in apoptotic cell death (Sipkens et al., 2013, 2011). Cysteine had been shown inactive on these parameters. Adenosine-2,3-dialdehyde treatment resulting in 17.7 nM intracellular SAH and 3.1 μM l-Hcy S-adenosylhomocysteine (SAH) was shown to induce induced apoptosis via activation of NOX2, p47phox, and NOX4 (Sipkens et al., 2012). Although the limitation of the study was the use of relatively high compared to physiological concentrations of Hcy, the short-term exposure (6 h) 10 mM Hcy may reflect a life-long exposure to moderately elevated levels of Hcy.

Hcy suppresses activity of endothelial nitric oxide synthase (eNOS) and cellular arginine transport resulting in decreases bioavailability of nitric oxide (Jin et al., 2007; Signorello et al., 2009). The inhibition of eNOS induces endothelial-to-mesenchymal transition characterized by the loss of cell polarity and endothelial specific morphology and acquisition of myofibroblast-like features (O'Riordan et al., 2007). This in turn leads to microvascular rarefaction and myocardial fibrosis that triggers the development of tissue hypoxia. Lowered bioavailability of NO leads to arterial stiffness. Hcy induced inactivation of eNOS results in reduced protein S-nitrosylation in human umbilical vein endothelial cells (HUVEC) and endothelial S-nitrosylation of aorta (Chen et al., 2014). Reduced S-nitrosylation of NADPH oxidase results in generation of ROS in human microvascular endothelial cells (Selemidis et al., 2007). Furthermore, S-nitrosylation of thioredoxin 1 at its Cys^{69} residue is vital for the redox regulatory and ROS scavenging activity (Haendeler et al., 2002). Additionally, Hcy triggers the cleavage of poly(ADP-ribose) polymerase (PARP) in cardiomyocytes and increases intracellular generation of peroxynitrite (Levrand et al., 2007). Increased production of ROS and decreased bioavailability associates with lipid peroxidation (De Bree et al., 2002). Homocysteine may also interact with cholesterol cytotoxicity by oxidative modification of LDL. However, there is no evidence of association between Hcy and cholesterol. Analysis of atherogenic lipids from The Very Large Database of Lipids database showed that hyperhomocysteinemia is not associated with an atherogenic lipid profile including triglycerides and the cholesterol concentration (Lupton et al., 2016). Results of clinical study showed that subjects with plasma homocysteine level over 15 μmol/l and lower folic acid level had higher excretion rate of products of arachidonic acid peroxidation such as F2-isoprostane 8-iso-prostaglandin F2α (8-iso-PG F2α) (Dragani et al., 2012). The subjects with high homocysteine level had high urinary level of 11-dehydrothromboxane B2 (11-dehydro-TXB2) indicating platelet activation in patients with HHcy. MTHFR C677 T polymorphism was associated with higher plasma Hcy (17.5 μmol/l vs. 12.9 μmol/l in non-carriers) and high urinary concentrations of 8-iso-PG F2α and 11-dehydro-TXB2. Folic acid supplementation lowered the level of homocysteine and subsequently down-regulated lipid peroxidation and platelet activation. Results of experimental and clinical studies showed that homocysteine-mediated oxidative stress triggers platelet activation leading to thrombosis. HHcy increases the sensitivity of platelets to adenosine diphosphate (ADP) and thrombin leading to platelet activation Mohan (Mohan et al., 2008; Riba et al., 2004). In rats treated with high methionine diet, moderate HHcy in rats was reported to increase the aggregation of platelets and enhanced thromboxane synthesis creating pro-thrombotic state (Durand et al., 1996).

Increased production of ROS distorts Hcy flux further since the key enzymes of methionine-homocysteine metabolism such as homocysteine folate-dependent remethylation and transsulfuration are redox sensitive. Oxidizing conditions inhibit methionine synthase catalyzed

remethylation of homocysteine (Chen et al., 1995). It was also reported that SAH is the cause of Nox-mediated ROS production and hyperhomocysteinemia induced cell death (Harrington et al., 2000; Lin et al., 2008; Sipkens et al., 2012). Recently, it was reported that inactivation of CBS is mediated by peroxynitrite (ONOO-) induced nitration at certain tyrosine residues (Tyr^{163}, Tyr^{223}, Tyr^{381} and Tyr^{518}) (Wang et al., 2017a). On the other hand, S-glutathionylation of CBS at Cys^{346} accounts for upregulation of CBS under conditions of oxidative stress (Niu et al., 2015). Functional studies of CBS showed that coordination of Cys^{52} to the heme iron is crucial for full activity of this enzyme. Displacement of Cys^{52} was proposed as a mechanism for CBS inactivation (Pazicni et al., 2005).

Accumulation of homocysteine has a direct effect on the tone and vasoactive responses of arterioles. The study using isolated arterioles has shown that 100 μM homocysteine decreased the arteriolar smooth muscle (Jud et al.) in a mode similar to the voltage-operated Ca^{2+} channel inhibitor nitrendipine thus affecting dilation of arterioles (Ungvari and Koller, 2001). Oxidative stress transduces matrix metalloproteinases (MMP) activation and promotes endothelial-smooth muscle disconnection/uncoupling. Animals study showed that hyperhomocysteinemia caused elevated superoxide levels and impaired responses to endothelium-dependent vasodilators in cerebral arterioles (Dayal et al., 2017). The cross-sectional area of the pial arteriolar wall were markedly increased. Hyperhomocysteinemia induces and potentiates endothelial dysfunction via μ-calpain activation (Cheng et al., 2015).

Hcy metabolite, homocysteine thiolactone, substantially enhances the activity of gp91(phox) subunit of NADPH oxidase, Nox2 and Nox4 (Murray et al., 2015; Sipkens et al., 2013; Zhang et al., 2010, 2011). Smith RM et al. using abdominal aorta from New Zealand White rabbits showed that 0.55 μmol/L homocysteine thiolactone reduced response to acetylcholine, whereas inhibition of Nox1 prevented acetylcholine induced blood vessel relaxation caused by HcyT (Smith et al., 2015). Inhibition Nox2 had no effect on acetylcholine induced blood vessel relaxation caused by HcyT. These data suggest that NADPH oxidase isoforms possibly perform diverse functions in homocysteine thiolactone induced blood vessel dysfunction. The experimental evidence indicate that Hcy promotes platelet accumulation at the site of endothelial injury, primarily through oxidation type reactions, and thus aggravating endothelial injury (Malinowska and Olas, 2011; Malinowska et al., 2012).

3.1.3. Homocysteine lowering therapy

The clinical benefit of homocysteine lowering B vitamin therapy is controversial. It was reported that Hcy lowering trials are ineffective for preventing cardiovascular diseases (Debreceni and Debreceni, 2012). A meta-analysis conducted by using data combined from 11 large trials with total of 22,000 participants, showed that lowering of homocysteine by using B vitamins had no effect on cognitive function or on cognitive aging (Clarke et al., 2014). However, high intake of folate and vitamin B6 was associated with reduced risk of mortality from heart failure in men and coronary heart disease in women in 14 years follow-up Japan Collaborative Cohort study with total 23,119 men and 36,611 women 40–79 years old (Cui et al., 2010). In another meta-analysis involving 8234 patients 49–72 years old with chronic kidney disease, lowering homocysteine with folic acid showed 10% reduction in incident of cardiovascular disease (Qin et al., 2013). In VITAmins TO Prevent Stroke (VITATORS) and Heart Outcomes Prevention Evaluation-2 (HOPE-2), the group of participants receiving folic acid in combination with D vitamins had lower incidence of myocardial infarction, vascular death and stoke (Park et al., 2016). Meta-analysis of individual patient data from two large trials of B vitamin therapy (VITATOPS and Vitamin Intervention for Stroke Prevention (VISP)) showed that patients with impaired renal function did not benefit from therapy with B12 vitamin for the prevention of stroke, whereas patients with normal renal function benefited from B12 treatment (Spence et al., 2017). Spence JD suggested that elderly patients with atrial fibrillation and metabolic B12 deficiency should be treated with methylcobalamin to reduce the risk of stroke and delay dementia (Spence, 2017). Meta-analysis of 14 prospective 10.7 years follow-up studies had shown inverse relation between daily supplementation of 200 μmol folic acid and incidence of coronary heart disease (Wang et al., 2012). A population-based study of Chinese adults with hypertension showed that 20% decline in total serum homocysteine reduced the risk of stroke by 7% (Huang et al., 2017). In China Stroke Primary Prevention Trial with total 20,702 participants with HHcy and hypertension 45–75 years old, combination therapy with 10 mg enalapril and 0.8 mg folic acid reduced the incident of first stroke and composite outcome of cardiovascular death as compares with enalapril alone (Huo et al., 2015). In the sub-study, the combination therapy resulted in greater drop in serum homocysteine level as compared with the enalapril alone and significantly reduced the risk of renal function decline in patients with chronic kidney disease (Xu et al., 2016).

The drugs used to control atrial fibrillation (blood thinner warfarin) and hypertension can cause nutrient deficiencies, including deficiency of folate, vitamins B6 and B12. The study evaluating the prevalence of hyperhomocysteinemia in patients four weeks after discontinuation of warfarin therapy showed elevation in plasma homocysteine accompanied by significant drop in the level of folate in 38.5% of participants (Sobczynska-Malefora et al., 2003). The analysis revealed a significant positive association between plasma total homocysteine and duration of warfarin therapy suggesting a need for nutritional therapy to complement the treatment of atrial fibrillation.

3.2. Neurodegeneration

Most common form of dementia in patients over 65 years is Alzheimer's disease (AD). The rate of dementia and AD continues to increase involving approximately 25%–50% of people aged 75 years and older (Duthey, 2013; Troesch et al., 2016). Elevated level of homocysteine is a risk factor for developing Alzheimer's disease (Gandy, 2012; Morris, 2003). It was reported that elderly persons who had Hcy level greater than 14 μM/L had an 82% higher incidence of stroke over 10 years period and have nearly doubled the risk of developing AD than did participant with lower levels of Hcy (Bostom et al., 1999; Moustapha and Robinson, 1999; Seshadri et al., 2002). High Hcy levels were shown to associate with poor executive function /language score in healthy non-demented very elderly (over 80 years of age) people (West et al., 2011). However, Hcy level was not associated with memory score in these individuals. The increase of homocysteine baseline by 1 μM/L corresponded to 6–7% rise in risk of stroke (Bots et al., 1999). Hyperhomocysteinemia causes cognitive dysfunction and memory deficit (Streck et al., 2004). Increase in Hcy level by 5 μM/L increase the risk of AD by 40% (Seshadri et al., 2002). AD subjects show on brain MRI the pattern of atrophy and white matter hyperintensities. Raised baseline levels of homocysteine in elderly associates with a faster rate of atrophy of the medial temporal lobe in patients with AD, rapid atrophy of the total brain volume in those with mild cognitive impairment and progression of ventricular enlargement (Clarke et al., 1998; Narayan et al., 2011; Smith et al., 2010). It was suggested that accumulation of homocysteine amplifies the negative impact of hypertension on cognitive function and in particular on progression of total white matter hyperintensity volume reflecting brain volume changes (Hooshmand et al., 2016; Iadecola, 2014; Kloppenborg et al., 2014). Population-based study conducted at Swedish National Study on Aging and Care in Kungsholmen (SNAC-K) showed that increased total homocysteine levels associates with increased rates of total brain volume loss over 6 years period among persons aged 60 years or older and with the progression of white matter hyperintensity among persons aged 60 years or older with hypertension (Hooshmand et al., 2016). The clinical studies using 1H magnetic resonance spectroscopy revealed that the brain of AD patients contains less N-acetylaspartate and more

myo-inositol, compared to cognitively healthy elderly subjects, and that the concentration of these two neurochemicals is correlated with the decline in cognitive performance (Duarte et al., 2014). A higher homocysteine level was found to correlate with a lower N-acetylaspartate concentration in the left hippocampus in elderly women but not in elderly men (Chen et al., 2011). 3D surface-based mapping of cortical gray matter distribution (thickness, volume, surface area) in elderly subjects with higher plasma levels of homocysteine from the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset revealed lowering gray matter thickness in bilateral frontal, parietal, occipital and right temporal regions (Madsen et al., 2015). It was shown that changes in Hcy directly related to nearly all the white matter integrities (Lee et al., 2017). Changes in posterior part of the brain highlight the vulnerability of patients with HHcy to neuronal degeneration.

3.2.1. Cerebrovascular events

There is increasing evidence that cerebrovascular disease plays a role in progression of dementia and Alzheimer's disease (Nelson et al., 2016). Clinical manifestations of Alzheimer's disease result from a combination of cerebrovascular disease and neurodegeneration (Malojcic et al., 2017). Cerebrovascular changes are common in aged subjects with dementia (Villeneuve et al., 2014). The level of Hcy greater than 14 μmol/l was associated with progression of aortic arch atheroma, which is independent risk factor for recurrent vascular events in stroke patients (Sen et al., 2010). Elderly patients who have had a stroke are twice as likely to develop dementia. Global brain perfusion analysis in a group of healthy subjects aged 50–75 years old revealed inverse relation between homocysteine and brain perfusion (Henriksen et al., 2014). Reduced cerebral autoregulation and impaired microcirculation affects amyloid-β clearance, thereby promoting cerebrovascular amyloid-β deposition (Brickman et al., 2015; Kuznetsova and Schliebs, 2013).

The prevalence of leukoaraiosis or white matter lesions increases with age from 50.9% in healthy persons aged 44 to 48 years to 95% in healthy persons over 60 years old (de Leeuw et al., 2001; Hachinski et al., 1987; Lin et al., 2017; Longstreth et al., 1996; Wen et al., 2009; Xiong and Mok, 2011). A positive correlation was reported between homocysteinemia and the age among men with large ischemic stroke but not women (Damelan et al., 2010). The logistic regression analysis showed that women aged 76.02 (+/- 12.93) tended to have more cardioembolic strokes while men aged 72.68 (+/- 13.27) had lacunar and atherosclerotic strokes more often (Caso et al., 2010). However, at multivariate analysis, female gender was not an independent factor for negative outcome. The level of homocysteine reached 23.0 μmol/L in male patients with lacunar stroke and 32.8 μmol/L with ischemic leukoaraiosis, which combines radiologically indicated leukoaraiosis with clinical lacunar stroke. The high prevalence of leukoaraiosis after stroke was recorded in the patients with HHcy (Vermeer et al., 2007). Functionally, cerebral small vessel disease, which is characterized by lacunar infarcts, microbleeds, leukoaraiosis, and a leaky blood-brain barrier, is an important cause of a cognitive decline and dementia (McCarty, 2015). Cerebral small vessel disease patients with leukoaraiosis was reported to have a significantly higher homocysteine levels reaching 23.7 μmol/L than those without leukoaraiosis (20.1 μmol/L) (Ma et al., 2010; Piao et al., 2018). Hcy associates with progression of cerebral small vessel disease and may serve as predictive factor (Feng et al., 2013; Piao et al., 2018; Wang et al., 2017c). The NAME (Nutrition, Aging, and Memory in Elders) study showed that the odds of a small vessel cerebral vascular disease were inversely related with the plasma choline concentration, which was positively associated with plasma total homocysteine, in elderly living in the greater Boston, Massachusetts, area and aged ≥60 years (Roe et al., 2017). Within a Japanese cohort of participants aged 67.2 ± 8.4 years, highest total Hcy (above 10.8 μmol/L) was associated with estimated glomerular filtration rate (eGFR) decline and the prevalence of lacunar stroke defined as a focal lesion > 3 mm and < 15 mm, abnormalities in the white matter (Miwa et al., 2016). High level of Hcy associated with the risk of incident cerebrovascular events such as ischemic stroke and hemorrhagic stroke. The 7.3 years survival analysis of dementia-free rate showed that patients with the higher total Hcy level were more likely to progress to all-cause dementia. Mild to moderate loss of renal function associated with accumulation of homocysteine associates with cerebral microangiopathy (small vessel disease) and macroangiopathy (Bang et al., 2016).

3.2.2. Vitamin micronutrient status

Elderly subjects are vulnerable from the nutritional point of view that increased risk of cognitive impairment, less defense against infections and higher mortality. High levels of Hcy and low levels of vitamin B12 and folate are common in the elderly and are associated with a variety of disorders, including cardiovascular and cerebrovascular conditions (Hooshmand et al., 2013; Kalita and Misra, 2015; Stabler, 2013). Decrease in vitamin B12 or folate levels lead to brain structural changes and increased rate of brain atrophy (Firbank et al., 2010; Jochemsen et al., 2013; Kloppenborg et al., 2014; Narayan et al., 2011; Snowdon et al., 2000; Vogiatzoglou et al., 2008). A progression of white matter lesion volume was linked to lower levels of vitamin B12 and holotranscobalamin but not accumulation of homocysteine (Hooshmand et al., 2013; Vogiatzoglou et al., 2008). Lowering of homocysteine level with vitamin B12 slow down the rate of atrophy (Smith et al., 2010). Cognitive impairment associated with HHcy in elderly has been shown, by some, to be protected by the use of folate and vitamin B12 (Blasko et al., 2012; Clarke et al., 2014). However, the effectiveness of this protection has been disputed (McCaddon and Miller, 2015). Spencer and Hachinski argued that in early trials the benefit of B Vitamins was obscured in elderly participants with renal impairment (Spence and Hachinski, 2018). Recently it was shown that folic acid supplementation resulted in significant reduction in first stroke risk in Chinese hypertensive subjects 55–65 years of age who had high Hcy level and low platelet counts (Kong et al., 2018). This study shows that folate fortification can be used for prevention of stroke and delaying dementia in elderly people.

Epidemiological studies have shown that AD patients have increased plasma levels of Hcy and diminished levels of B6 and B12 vitamins and folic acid (Coppede et al., 2012; Mohajeri et al., 2015). Low folate and low B vitamins diet causes neuronal dysfunction leading to short term memory loss (Nuru et al., 2018). Polymorphism of MTHFR was associated with changes in the morphology of gray matter in posterior cingulate cortex-anchored covariance (Chang et al., 2017). Although, polymorphism of MTHFR seems to contribute to late onset of AD, no relation has been found between MTHFR polymorphism and cognitive performance or severity of cerebral white matter lesions (Coppede et al., 2012; de Lau et al., 2010). Recent data show vitamin B6 and B12 supplementation slow down grey matter atrophy of specific brain regions that are a key component of the AD and associated cognitive decline (Douaud et al., 2013). These observations support the concept that blood homocysteine and the B vitamins that influence the level of homocysteine are potentially causal and modifiable risk factors. However, there is no conclusive evidence to suggest that vitamin B12 supplementation can prevent development of AD. New stroke prevention guideline offers approach to lifestyle modification including physical activity, diet and nutrition, smoking cessation, obesity and dyslipidemia (Meschia et al., 2014). The use of the B complex vitamins, B12 and B6, folic acid was recommended for prevention of ischemic stroke in patients with HHcy. Novel oral anticoagulants in patients with nonvalvular atrial fibrillation were recommended based on randomized trials of each oral antocoagulant vs warfarin.

Recent study has shown that in AD patients the prevalence of high level of Hcy (16–20 μmol/l) associated with high incidence of vitamin D-OH25 and folic acid deficiency (Moretti et al., 2017). In healthy old population, there was low prevalence of vitamin D-OH25 and folic acid deficiency. Serum levels of vitamin D-OH25 were found to be significantly and directly correlated with low levels of folate in the vitamin

D-deficient group. It was suggested that co-existence of low levels of vitamin D and high levels of homocysteine might be responsible for altered response to inflammation, and, therefore, predispose to microvascular damages. These observations suggest that vitamin D supplementation in combination with folic acid may improve cognitive function in elderly people and may help prevent Alzheimer's disease and dementia.

3.2.3. Mechanism of homocysteine-related nerodegeneraton

Hcy exerts neurotoxicity by suppressing activities of multiple enzymes including Na+, K + ATPase, superoxide dismutase (SOD), glutathione peroxidase (GPx) and diminishing glutathione content (Longoni et al., 2016). Hcy and its metabolites enhance the activity of gp91(phox) subunit of NADPH oxidase isoforms, Nox2 and Nox4 (Murray et al., 2015; Sipkens et al., 2013; Zhang et al., 2010, 2011). Activation of Nox increases production of ROS that causes activation of glial cells. In microglia, Hcy activates Nox2 NAD(P)H oxidase by the phosphorylation of regulatory subunit p47phox leading to cellular proliferation and activation of microglia (Zou et al., 2010). Disruption of redox balance and excessive generation of ROS promote neuronal cell death in cerebral cortex. Cortical astrocytes exhibit the greatest sensitivity to Hcy toxicity (Jin and Brennan, 2008; Maler et al., 2003). ROS generation is responsible for activation of nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3 (NLRP3) inflammasomes (Fig. 6) (Ding et al., 2014). Similarly, hyperhomocysteinemia leads to activation of NLRP3 inflammasomes (Abais et al., 2014; Conley et al., 2017; Zhang et al., 2010). The innate immune sensor, NLRP3 inflammasomes control caspase 1 and ROS mediated secretion of IL-1β and IL-18 which trigger inflammation (Krishnan et al., 2014; Yin et al., 2017). Activation of NLRP3 inflammasome contributes to age-related cognitive impairment, bone loss, muscular degeneration and susceptibility to pulmonary fibrosis (Chen et al., 2015; Kauppinen et al., 2016; Ma et al., 2018b; Stout-Delgado et al., 2016; Wang et al., 2017b). Homocysteinemia mediated inflammation is associated with brain atrophy and several neurodegenerative disorders including AD (Scott et al., 2004).

Homocysteine impaired nitric oxide synthase activity causing endothelial dysfunction, thus increasing the risk of cardiovascular or cerebrovascular events (Hooshmand et al., 2013). Cerebral small vessel disease is characterized by hypertrophy of cerebral arterioles and the loss of adaptive vasodilation (McCarty, 2015). Rodent studies strongly suggest that activation of NOX2 leads to structural and functional derangements of cerebral arterioles, in part due to impairment of endothelial nitric oxide synthase (eNOS) activity. Activation of Nox2-dependent NADPH oxidase activity and impairment of endothelial nitric oxide synthase (eNOS) activity is a crucial driver in cerebral small vessel disease, a common feature of aging brain, which show lacunar infarcts, microbleeds, leukoaraiosis, and a leaky blood-brain barrier. In the cystathionine beta-synthase knockout mouse model, elevations in total plasma homocysteine caused structural alteration in cerebral microcirculation due to activation of Nox and generation of ROS (Lominadze et al., 2012).

The neuronal cell death induced by Hcy is also attributed to the over-stimulation of N-methyl-D-aspartate (NMDA) receptors, oxidative stress and release of cytochrome c (Ho et al., 2001; Kruman et al., 2000; Lipton et al., 1997). Hcy and product of its spontaneous oxidation, homocysteic acid, are endogenous agonists of metabotropic glutamate receptors operating via the glutamate binding sites of the NMDA receptors (Bolton et al., 2013; Lipton et al., 1997; Parsons et al., 1998; Shi et al., 2003). Hcy shows high affinity for GluN1/2 A NMDA receptors with EC50 of 9.7 ± 1.8 (Sibarov et al., 2016). Persistent activation of NMDA receptor channels mediates enhanced excitatory synaptic transmission and triggers neurodegenerative cascades activated by excessive Ca^{2+}. Activation of extrasynaptic NMDA receptors modifies amyloid precursor protein expression and increases formation of amyloid-β (Bordji et al., 2010).

Hcy increases NFκB expression in astrocytes in cerebral cortex in a dose-dependent manner (Longoni et al., 2017). The enhanced release of tumor necrosis factor- α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) can lead to neuroinflammation, which is commonly associated with age-related neurodegenerative disorders such as vascular dementia (Scherer et al., 2014). TNF-α is involved in synaptic scaling whereby low extracellular glutamate triggers release of the cytokine from astrocytes and promotes the surface expression of postsynaptic glutamate receptors (Beattie et al., 2002). Hyperhomocysteinemia is associated with increased levels of TNF-α, IL-1β, IL-6, and the chemokine monocyte chemotactic protein-1 (MCP-1) in the hippocampus, as well as an increase in IL-1β and IL-6 levels in cerebral cortex (Scherer et al., 2014). Chronic mild hyperhomocysteinemia enhances acetylcholinesterase (AChE) activity in the cerebral cortex leading to a proinflammatory state. Enhanced release of IL-1 and IL-6 correlates with impaired neurogenesis, memory loss and an increased risk of myocardial infarction and diseases of coronary arteries (Gokkusu et al., 2010; Harris et al., 1999; Holven et al., 2006; Jones and Thomsen, 2013). In rats, chronic hyperhomocysteinemia increases pro-inflammatory cytokines (TNF-a, IL-1β, IL-6) and chemokines in

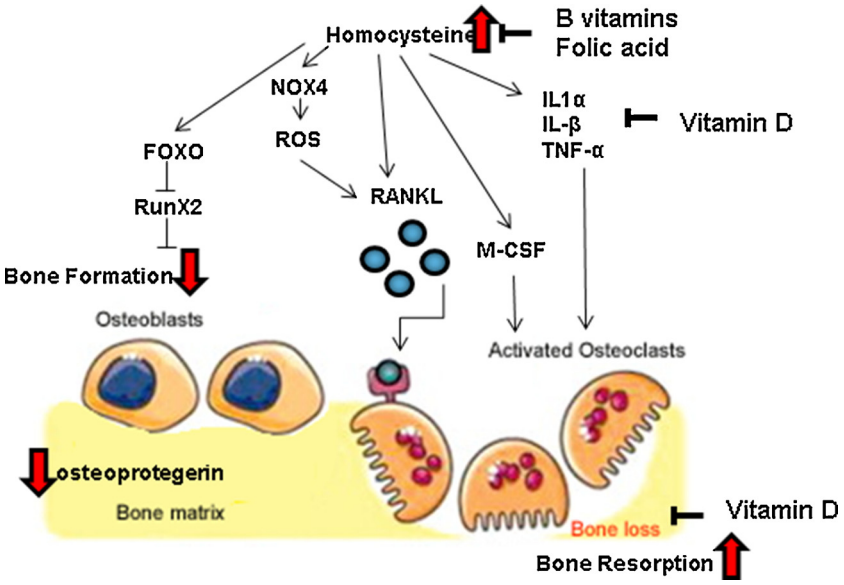

Fig. 6. A simplified scheme of mechanism of homocysteine induced bone resorption. In the presence of homocysteine, the receptor activator of NF-kB ligand (RANKL) binds to the receptor RANK at the surface of osteoclasts and induces osteoclastogenesis resulting in bone loss. Vitamins prevent collagen degradation and make stronger bone structure.

hippocampus and serum (da Cunha et al., 2012).

Hcy decreases HO-1 expression levels in astrocytes in cerebral cortex in a dose-dependent manner (Longoni et al., 2017). However, pronounced HO-1 immunoreactivity was reported in neurofibrillary tangles, senile plaque neurites, neuropil threads and granulovacuolar degeneration in brain of patients with AD (Barone et al., 2014; Smith et al., 1994). The number of glial fibrillary acid protein (GFAP)-positive astrocytes that expresses HO-1 is markedly increased in the hippocampus and cerebral cortex in patients with AD as compared to age-matched non-demented controls (Gupta et al., 2014; Schipper and Song, 2015). Enhanced up-regulation of glial HO-1 and CO production are considered an important mechanism driving the cognitive impairment. It is possible that under conditions of overactivation of HO-1, CO that is generated may target heme-containing proteins such as cytochromes, guanylyl cyclase and CBS. CO binds to CBS with binding constant being in the range of 1.5–68 μM (Puranik et al., 2006). The binding of CO to the heme iron leads to the loss of CBS activity (Shintani et al., 2009; Taoka et al., 1999).

Homocysteine accumulation has an amyloidogenic effect by inducing endoplasmic reticulum-localized membrane protein HERP and activating caspase-3 that result in accumulation of β-amyloid 1–40 peptides (Chung et al., 2016; Seshadri et al., 2002). High Hcy was shown to increase expression and activity of 5-lipoxygenase (5-LO) that contribute to the amyloidotic phenotype of the AD (Di Meco et al., 2018; Li et al., 2017). Diet induced accumulation of Hcy is associated with increased S-adenosylhomocysteine/S-adenosylmethionine (SAH/SAM) ratio (Dziegelewska et al., 2016). Hcy reduces levels of DNA methyltrasferases (DNMT1, DNMT3a, and DNMT3β) and leads to hypomethylation of 5-lipoxygenase gene. Overexpression of S-adenosylhomocysteine hydrolase (SAHH) prevents Hcy induced activation of 5-LO and formation of β-amyloid oligomers. CBS deficient mice, which spontaneously develop hyperhomocysteinemia, exhibit significant increase in 5-LO protein and mRNA levels (Di Meco et al., 2018; Li et al., 2017). It was shown that Hcy directly influences 5-LO expression via hypomethylation of 5-lipoxygenase promoter. The effect of Hcy on the 5-LO enzymatic pathway was secondary to 5-LO transcriptional upregulation. In vitro studies confirmed these results and demonstrated that the mechanism involved in the Hcy-dependent 5LO activation and amyloid β formation is DNA hypomethylation secondary to the elevated levels of SAH. Taken together these findings represent the first demonstration that induced activation of 5-LO contributes to an inflammatory response. The 5-LO and its downstream leukotriene metabolites have long been known to be important modulators of oxidation and inflammation.

The cerebrovascular permeability is increased in Cbs+/- mice model of hyperhomocysteinemia due to activation of MMP-2, MMP-9, and MMP-13 (Kumar et al., 2008; Lominadze et al., 2012; Muradashvili et al., 2014). Hcy induced activation of MMPs was attributed to activation of NADPH oxidase and oxidative stress. The increase in cerebrovascular permeability contributes to formation of fibrinogen-β-amyloid complex that is associated with neuroinflammation leading to loss of memory.

Hcy neurotoxicity is mediated by its metabolite, homocysteine thiolactone (HTL) that causes post-translational modification of proteins. It was shown that HTL-modified cytochrome c causes conversion of the hexa-coordinate cytochrome c to a penta-coordinate species leading to conformational alterations that affect the packing of the apolar groups. Such changes allow reduction of the heme moiety and results in activation of peroxidase-like function of cytochrome c (Sharma and Singh, 2017). Accumulation of Hcy and HTL was implicated in aberrant protein folding and deposits of protein aggregates so-called “amyloidosis”. Despite the relatively low plasma concentration, HTL is characterized by extreme chemical reactivity. HTL binds to various proteins via non-enzymatic reactions resulting aberrant functions of targeted proteins. HTC mediated N-homocysteinylation predispose β-amyloid aggregation and deposition (Khodadadi et al., 2012). In AD patients with hyperhomocysteinemia, the level of β-amyloid deposits is substantially increased in the blood vessels and brain parenchyma. Hcy and HTL jointly enhance the interaction between fibrinogen and β-amyloid hence promoting the formation of tighter fibrin clots (Chung et al., 2016).

4. Kidney dysfunction

At cellular level, there is age associated decline in cell functions in different tissues. In kidney, age related structural and functional changes lead to decline in glomerular filtration rate (GFR), podocyte dysfunction and apoptotic cell death, changes in tubular reabsorption and secretory capacities, and dysfunction of glomerular barrier. GFR declines with age, even in people without kidney disease. Although, the filtration fraction remains constant until about age 65, it drastically declines from the age of 70 (Denic et al., 2016; Glassock and Winearls, 2009; Hommos et al., 2017). There are only about 48% intact nephrons remain in the aged kidney by age 70 to 75 in healthy elderly as compare to young people aged 18 to 29 years (Denic et al., 2017; Schmitt and Melk, 2017). The progressive reduction in the number of viable and function podocytes, along with decreased capacity for their regeneration and repair leads to deterioration of the integrity of slit pore membrane in glomeruli affecting kidney GFR. MTHFR gene polymorphism contributes to nephropathy and progression of chronic kidney disease (CKD) (Bloudickova et al., 2014; Dessi et al., 2015). CKD has been proposed as an independent risk factor for cardiovascular disease and cognitive impairment in the elderly (Etgen et al., 2012). Association was shown between kidney dysfunction and lower global, frontal, parietal, temporal, occipital, and insular lobar cortical thickness in non-demented elderly persons (Chen et al., 2017). Interestingly, low GFR is seen in patients with brain atrophy (Knopman et al., 2008; Yakushiji et al., 2010). Impaired renal function causes accumulation of uremic toxin indoxyl sulfate that was shown to contribute to neurodegeneration (Adesso et al., 2017; Arnold et al., 2016). Uremic toxins also induce kidney fibrosis by triggering epithelial-to-mesenchymal transition (Sun et al., 2012). Endothelial-to-mesenchymal transition of glomerular vascular endothelial cells is considered crucial in development of nephropathy (Cruz-Solbes and Youker, 2017; Zhang et al., 2011). In turn, renal insufficiency causes further impairment of homocysteine metabolism.

Plasma Hcy concentration is partly determined by renal plasma clearance. In hypertensive patients, the fractional extraction of Hcy across the kidney is positively related to renal plasma flow. Most people over the age of 65 suffer from some degree of kidney dysfunction. In the aging kidney, there increased intimal cell proliferation in preglomerular arterioles, increased intrarenal shunting and capillary bypassing predominantly affecting the cortex (O’Sullivan et al., 2017). Microvascular rarefaction, hypoxia, fibrosis and inflammation contribute to glomerular sclerosis with aging. Such changes affect glomerular filtration rate and may be responsible for increased level of homocysteine with age. Higher homocysteine level promotes a greater decline of GFR and development of kidney disease (Ninomiya et al., 2004).

Patients with CKD are at an increased risk of ischemic and hemorrhagic stroke (Seliger et al., 2003). Estimated glomerular filtration rate (GFR) or proteinuria (albumin/creatinine ratio = 30 μg/mg) is seen in patients with dementia and cognitive decline (Barzilay et al., 2008; Elias et al., 2009; Kurella et al., 2005; Kurella Tamura et al., 2008). CKD was associated with a rapid rate of global cognitive decline in about 3.4 years (Bennett et al., 2005). Deficiency of vitamin B12 is most common in seniors. Approximately 20% of elderly have B12 deficiency and the percentage increases with age. It was reported that more than 30% of patients aged over 71 years old have B12 deficiency (Spence, 2006). The marked decline in renal function with age increases the prevalence of vitamin B12 deficiency and results in high levels of Hcy (Spence, 2009). Folic acid supplementation was shown to reduce Hcy induced oxidative stress and to improve hyperhomocysteinemia associated renal

dysfunction (Hwang et al., 2011). Folic acid lowers concentration of Hcy and thereby attenuates NADPH oxidase activity and protects podocytes from oxidative functional damages (Hwang et al., 2011). It is also effective in suppression of superoxide producing xanthine oxidase and reactivation of SOD.

4.1. Mechanism of homocysteine-related kidney dysfunction

Age associated hyperhomocysteinemia induces hemodynamic dysfunction in kidneys by compromising the attachment and functions of podocytes. Hcy induces damage of podocyte and subsequent glomerular fibrosis through activation of NADPH oxidase gp91(phox) subunit and increased ROS production (Zhang et al., 2011). ROS generation is responsible for NLRP3 inflammasome activation (Ding et al., 2014). Hyperhomocysteinemia leads to activation of NLRP3 inflammasomes (Abais et al., 2014; Conley et al., 2017; Zhang et al., 2010). The innate immune sensor NLRP3 inflammasome controls caspase 1 and ROS mediated secretion of IL-1β and IL-18 which trigger inflammation (Krishnan et al., 2014; Yin et al., 2017). Systemic inflammation in multiple organs, including kidney, heart and central nervous system is mechanism that underlie the age associated degenerative disorders (Martins et al., 2015). Chronic oxidative stress due to imbalance between tissue levels of ROS and antioxidant activity exacerbates damage in highly oxidative tissues such as heart, brain and kidney. Activation of NADPH oxidase is considered to be responsible for hyperhomocysteinemia-induced oxidative stress in the kidney. Hyperhomocysteinemia triggers Nox-dependent superoxide production in podocyte and mesangial cells causing cell injury and glomerulosclerosis (Wan et al., 2016). In the progression of CKD, the redox balance is tipped toward oxidation, due to decrease in expression of nuclear factor erythroid-2 related factor 2 (Nrf2) and its target genes encoding antioxidant enzymes, such as heme oxygenase 1 (HO-1) and SOD (Hishikawa et al., 2018). It was reported that homocysteic acid down-regulates Nrf2/HO-1 pathway (Tan et al., 2013). Homocysteine is known to repress SIRT1/AMPK pathway (Hung et al., 2015). SIRT1 is expressed in tubular cells and podocytes and has major role in kidney by regulating angiotensin II and therefore blood pressure and sodium water handling (Morigi et al., 2018). *Sirt1* deficiency enhances peritubular capillary rarefaction and perpetrates nephrosclerosis (Kida et al., 2016). In aging mice, reduction of SIRT1 was shown to accelerate kidney injury (Chuang et al., 2017).

Suppression of folate pathway and depletion of CBS both result in development of fibrosis (Hamelet et al., 2007; Martinelli et al., 2013). Folic acid protects podocytes from oxidative functional damages by lowering concentration of Hcy and thereby attenuating NADPH oxidase activity (Hwang et al., 2011). It is also effective in suppression of superoxide producing xanthine oxidase and reactivation of SOD.

In elderly, Hcy induces senescence in podocytes and renal tubular cells evidenced by increase in cellular senescence markers such as p16, p21 and p53, markers of oxidative stress and shortened telomere length (Zhang et al., 2015; Zhu et al., 2006). Hcy induced senescence might be responsible for insufficient repair and functional loss in kidney cells. Hcy accelerates cellular senescence by suppressing telomerase reverse transcriptase (hTERT) expression and reducing telomere activity (Zhang et al., 2015). Hcy mediated upregulation of hTERT repressor CTCF contributes to Hcy reduced methylation of hTERT promoter. L-arginine and L-arginine mimic, FA, was shown to almost completely reverse Hcy induced senescence in endothelial cells, whereas SAM treatment was less effective (Scalera et al., 2006). Aging is associated with depletion and inactivation of CBS leading to hyperhomocysteinemia and induced premature senescence in human endothelial cells (Albertini et al., 2012).

5. Age associated bone disease

Osteoporosis in one of the most common diseases that influences quality of life and life expectancy in elderly people (Cauley et al., 2000). It is characterized by low bone mass and deterioration of bone tissue. The rate of bone loss increases dramatically in women 5–10 years after menopause and in men over age 65 leading to increase in incidence of osteoporotic fractures associated with disability and mortality (Alejandro and Constantinescu, 2018; Lin and Lane, 2006). Deficit in cognition promotes falls and fragility fractures (Jakob et al., 2014). The most common osteoporotic fracture sites are hip, wrist, and spine. Elevated Hcy has been a strong risk factor for hip fracture in elderly adults causing high morbidity and mortality (McLean et al., 2004). Risk of hip fracture doubles every five years after age 50. Men have lower prevalence rate in development of osteoporosis than women. However, a third of all hip fractures in seniors occur in men (Eastell et al., 1998; Orwoll and Klein, 1995). Elderly men with accelerated bone loss have low cortical thickness and low bone strength resulting in increased risk of fracture (Cauley et al., 2018). About 49% of elderly admitted to hospital with vertebral fragility fractures were previously diagnosed with osteoporosis (Levy et al., 2012).

Accumulation of homocysteine and depletion of Vitamins B contribute to deterioration of bone mineralization, microarchitecture and bone turnover (van Wijngaarden et al., 2013). A significant inverse relation has been found between serum Hcy concentration and bone mineral density (Herrmann et al., 2007; Holstein et al., 2011). A cross-sectional survey revealed strong association between homocysteine and bone turnover markers and lumbar bone mineral density in postmenopausal women (Bailey et al., 2015). Results from Longitudinal Aging Study Amsterdam and OPRA study showed a significant association between level of Hcy and bone mineral density in femoral neck and lumbar spine in elderly women (Dhonukshe-Rutten et al., 2005; Gerdhem et al., 2007). Subjects with concentration of Hcy over 15 μmol/l had higher urinary concentration of bone resorption marker, deoxypyridinoline. Positive correlation had been found between high concentrations of Hcy and SAH in bone and loss of bone structure in osteoarthritis patients aged 44–86 years undergoing hip arthroplasty (Holstein et al., 2011). Surprisingly, the increase in concentration of SAM was related to deteriorated cancellous bone structure. It was shown that 50% of Hcy in bone is bound to collagen that affects the formation of collagen crosslinks (Herrmann et al., 2007; Holstein et al., 2011). However, levels of SAM and SAH in circulation were not associated with the risk of osteoporotic fractures in elderly people (Enneman et al., 2012). Considering the significance of folic acid deficiency in HHcy, MTHFR polymorphism C667 T increases frequency of osteoporotic vertebral fracture incidence (Abrahamsen et al., 2003; Shiraki et al., 2008; Villadsen et al., 2005). Baines and co-authors reported that MTHFR C677 T polymorphism associates with the risk of fractures but not bone mineral density in postmenopausal women (Baines et al., 2007). However, the results from recently published meta-analysis have shown association between MTHFR C667 T polymorphism and reduced bone mineral density in lumbar spine and femoral neck in both women and men (Li et al., 2016). Single nucleotide polymorphism at 3′UTR region in the folate transporter gene, SLC25A32, associates with low plasma concentration or folate and higher rate of fracture incident in Japanese postmenopausal women (Urano et al., 2014).

5.1. Mechanism of homocysteine-related osteoporosis

The precise mechanism linking homocysteine accumulation to bone mass loss and increased fracture risk remains unclear. However, it is known that Hcy induced production of ROS plays an important role in osteoclastogenesis. Hcy mediated ROS production activates osteoclast differentiation (Blume and Curtis, 2011; Koh et al., 2006). Macrophage colony-stimulating factor (M-CSF) and membrane-bound receptor activator of nuclear factor-kappa B (RANK) ligand (RANKL), which is expressed by osteoblast-lineage cells, are required for the osteoclast development and osteoclast function (Park et al., 2017). Binding of RANKL with its receptor RANK in osteoclasts stimulates their

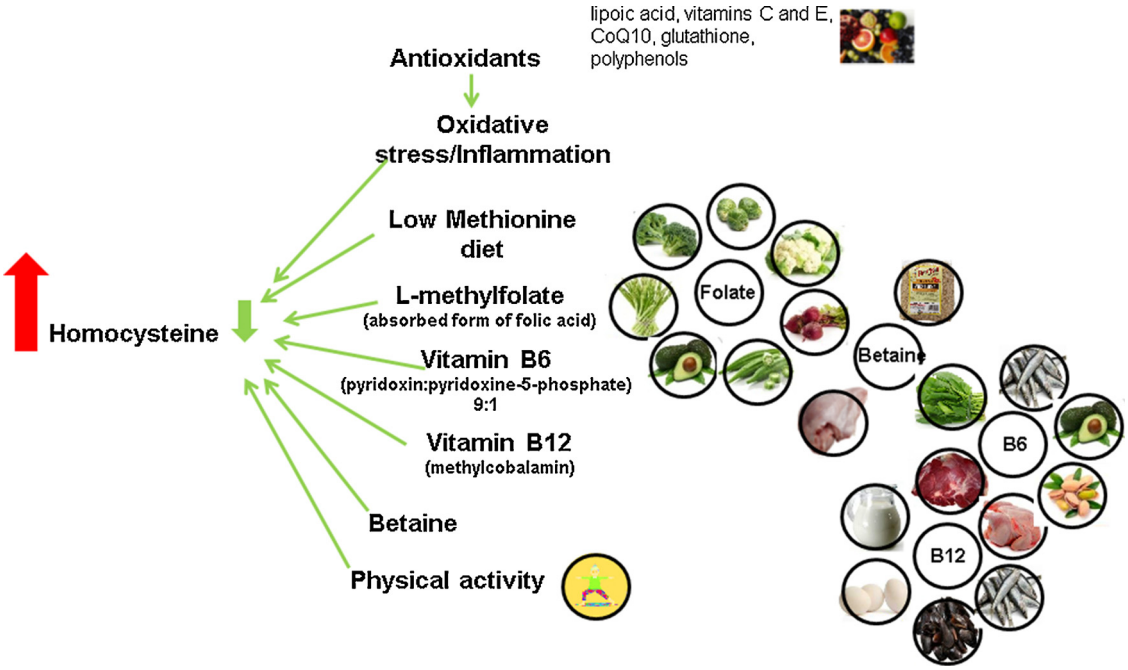

Fig. 7. Lowering homocysteine level.

differentiation and prevents osteoclast cell death. Hcy induced oxidative stress deranges insulin sensitive FOXO1 and MAPK signaling cascades leading to decreased osteoprotegerin (OPG) and increased RANKL synthesis in osteoblast culture (Vijayan et al., 2013). In rats, HHcy increased synthesis of proresorptive and inflammatory cytokines such as RANKL, M-CSF, IL-1a, IL-1b, and TNF-a shifting OPG:RANKL towards increased osteoclast activity and bone loss. Dysregulation of RANKL/RANK was reported in HHcy subjects (Nenseter et al., 2009). Increase in concentration of homocysteine activates osteoclasts leading to bone resorption (Fig. 7) (Herrmann et al., 2005; Koh et al., 2006). In rat model, HHcy results in reduction in femoral neck strength (Herrmann et al., 2007). Homocysteine at high concentrations inhibits the activity of lysyl oxidase that affects cross-linking of collagen and results in bone fragility (Herrmann et al., 2007; Liu et al., 1997; Lubec et al., 1996; Raposo et al., 2004; Thaler et al., 2011). Hcy induces apoptosis in primary human bone marrow stromal cells and osteoblastic MC3T3-E1 cells via increased production of ROS and activation of NF-kB (Kanazawa et al., 2017; Kim et al., 2006).

It was reported that Hcy acts as ligand to peroxisome proliferator-activated receptor gamma (PPARγ), which enhances osteoclastgenesis (Wan et al., 2007). Hcy binding to PPARγ and Hcy mediated oxidative stress via activation of NOX4 affect bone resorption (Mishra et al., 2010; Stunes et al., 2011). Accumulation of ROS results in activation of matrix metalloproteinases (MMPs), which are involved in matrix degradation. It was reported that Hcy disturbs bone metabolism via activation of MMPs (Vacek et al., 2013). HHcy delayed resorption of epiphyseal cartilage during endochondral ossification in developing rat embryo (Azizi et al., 2010). In animal model of HHcy, upregulation of MMP-13 and COX-2 contributed to cartilage degradation (Ma et al., 2018a). Treatment of chondrocytes with Hcy reduced SIRT1/AMPK/PGC-1α signaling resulting in elevated production of pro-inflammatory cytokines and induced pro-apoptotic responses.

High homocysteine levels can cause blood clots and decrease in bone blood flow leading to bone deterioration due to lack of nutrient delivery. Decrease in tibial flow and bone density was shown to associate with increased activity of NOX-4 and ROS production and decreased bio-availability of NO in heterozygous CBS+/- hyperhomocysteinemic mice (Tyagi et al., 2011a). The treatment with folic acid ameliorated these effects. In rats, it was shown that high concentrations of Hcy and SAH and increased SAH:SAM ratio tightly associated with impaired osteoblast differentiation and reduced bone mass (Herrmann et al., 2009; Vaes et al., 2010). In mouse lacking gastric intrinsic factor (GIF), which is required for the absorption of vitamin B12, vitamin B12 deficiency caused growth retardation and low bone volume due to decreased number of osteoblasts and impaired growth hormone (Roman-Garcia et al., 2014).

Homocysteine lowering therapy with vitamins B was shown to reduce the incidence of osteoporotic fractures (Sawka et al., 2007). It was reported that supplementation of folic acid (0.5–5 mg day^{-1}) reduced the levels of homocysteine in blood up to 25%; the co-supplementation of folic acid and Vitamin B12 (0.5–5 mg day^{-1} and 500 mcg day^{-1}, respectively) provided a reduction in serum total homocysteine by 32% (Robert, 1998). In the Hordaland Homocysteine study, folate was linked to a reduced risk of fracture in elderly (Gjesdal et al., 2006). Strong association was reported between folate level and vertebral mineral density in postmenopausal women (Cagnacci et al., 2008). However, the authors didn't observe any relation between the changes in bone mineral density and concentrations of Hcy and Vitamin B 12. In VITAmins To Prevent Stroke (VITATOPS) randomized trial, daily treatment with 2 mg of folic acid and B Vitamins (25 mg of vitamin B6 and 500 μg of vitamin B12) had no effect on the incidence of osteoporotic fractures in elderly patients with cardiovascular disease (Gommans et al., 2013). Another randomized controlled trial showed that supplementation with folic acid and Vitamins B6 and B12 could lower plasma Hcy but had no effect on bone resorption in healthy elderly people (Green et al., 2007). In one prospective trial, treatment with 5 mg of folic acid and 1.5 mg of Vitamin B12 for 2 years decreased the incidence of fracture by 75% (Sato et al., 2005).

6. Hearing loss

One of common health issues associated with aging is hearing loss. Presbycusis is the most common type of sensorineural hearing loss caused by aging of the auditory system that limits the quality of life. Conditions that are common in elderly people such as high blood pressure, diabetes, nutritional deficiencies can contribute to hearing loss. Various epidemiological studies have shown correlations between low B vitamins and folate status and increased plasma homocysteine,

and age associated hearing loss (Berner et al., 2000; Cadoni et al., 2004; Karli et al., 2013; Lasisi et al., 2010).

Elevated homocysteine has adverse effect on blood flow to the cochler and causes the cellular degeneration in inner ear thus leading to age associated hearing loss (Fattori et al., 2001; Martinez-Vega et al., 2015). In $CBS^{+/-}$ heterozygous mice, HHcy led to matrix remodeling in the cochlea (Kundu et al., 2009). The remodeling was caused by Hcy induced protein nytrotyrosination and activation of NOX subunit $p22^{phox}$ in cochlea. Hcy induced oxidative stress and reduction of vessel density was prevented by administration of folic acid. Randomized trials revealed that lowering of Hcy level by supplementation of folic acid delayed the progression of hearing loss (Durga et al., 2007).

7. Conclusion remarks

In recent years, there are numerous studies on life extension. Search for life extension is very costly and time consuming. However, a number of scientists and wealthy entrepreneurs have invested large resources towards anti-aging research. However, instead of looking for “fountain of youth”, it will be more desirable to extend human health span life. The screening for raised homocysteine level should be carried out in elderly subjects over 60 years old. Assessment of folate or of vitamin B12 status would be the most beneficial for those over 60 years of old to establish nutritional requirements. Furthermore, supplementary folate, vitamins B complex (B12 and B6), vitamin D and antioxidant and vitamin-rich diet must be recommended to all people over 65 years of age (Fig. 7). Folate and vitamins B complex must be recommended to patients with atrial fibrillation using warfarin and hypertension patients to prevent development of cardiovascular or cerebrovascular accident. Although, it remains unclear whether correction of hyperhomocysteinemia is able to prevent the development of vascular disease, homocysteine-lowering B vitamins and antioxidant therapy might be useful in lowering the risk of inflammation and vascular risk factors.

However, there will likely be novel pharmaceutical interventions to restore functions of enzymes involved in remethylation and transsulfuration of homocysteine.

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