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Chronic Formaldehyde-Mediated Impairments and Age-Related Dementia

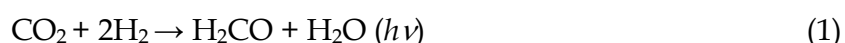
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1. Introduction

1.1 Formaldehyde (FA) in the human environment

FA (H₂CO), the simplest aldehyde (Kilburn, 1994), existed in the pre-biological atmosphere of the primordial earth (Canuto et al., 1983) and is also present in the outer galaxies (Blair et al., 2008). FA is believed to have been the first organic molecule, being derived from photochemical reactions between simple gas elements in the primeval earth's atmosphere (Reaction 1) (Pinto et al., 1980; Canuto et al., 1983).



FA is also a basic biological building block, and participates in the synthesis of amino acids such as glycine and alanine in aqueous medium (Miller, 1953; Sokolskaya, 1976; Sakurai&Yanagawa, 1984). It is involved in the generation of carbohydrates via the formose cycle in bacteria (Kalapos, 1999). FA is believed to form complex organic molecules (Canuto et al., 1983) and play a key role in the process of evolution (Kalapos, 1999).

As reported by the U.S. Environmental Protection Agency (June 18, 2010), FA is present in products such as abrasive materials, plywood adhesives, insecticides, insulation and embalming fluids. Anthropogenic production of FA is mainly from power plants, petroleum refineries, coking operations, incineration, motor vehicle exhaust, and tobacco smoke (He et al., 2010). This simplest aldehyde has become one of the highest risk factors in the pollution of the human environment.

1.2 Toxicity of exogenous formaldehyde and cognitive impairments

Due to its high reactivity, FA leads to the formation of stable methylene bridges between nucleic acids and the amines of proteins (Conaway et al., 1996), resulting in crosslinking between nucleic acids and/or proteins and their subsequent polymerization (Kast et al., 2008). Both the amino-terminals of proteins and residues containing ε-amino and thiol groups, such as lysine, arginine, histidine, cysteine, tyrosine and tryptophan, are modifiable

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targets of FA, and form methylol groups or Schiff-bases after modification (Metz et al., 2004). A number of reports have indicated that FA usually acts as a chemical crosslinker for biomacromolecules in cells. Exposure to FA at a concentration of 0.21 mM for 6 h reduces the growth rate of human bronchial epithelial cells to 50% that of controls due to FA depression of RNA synthesis and the formation of both DNA single-strand breaks and DNA-protein crosslinks (DPCs) (Saladino et al., 1985). When cultured with FA at concentrations of 0.1-0.3 mM, human lung A549 cells, primary human nasal epithelial cells and DT40 cells undergo the process of DPC formation (Nakamura et al., 2007; Speit et al., 2008). Treatment of rat aorta endothelial cells with FA at 0.01-2.00 mM promotes the formation of DPC, a potential risk factor in atherosclerosis (Yu&Deng, 1998; Zhang et al., 2006). FA has also been shown to induce chromosomal aberrations (CAs) and sister chromatid exchanges (SCEs) in cultured cells (Conaway et al., 1996). It is worth noting that FA has biphasic effects on cell lines depending on its concentration: enhancing apoptosis, necrosis and even causing cell death at high concentrations (>1 mM), while promoting cell proliferation at low dose (0.1 mM) (Tyihak et al., 2001).

Excess exposure to exogenous FA can induce carcinogenesis and cardiovascular dysfunction, possibly due to the formation of DPC (Shaham et al., 2003). Inhalation of FA vapor at concentration of up to 0.50 mM can cause rhinitis, epithelial dysplasia, squamous metaplasia, and even squamous cell carcinomas in rodents (Swenberg et al., 1980). Similar results have also been observed in a study on monkeys exposed to FA at 0.20 mM (Conaway et al., 1996). Tumor generation has been observed in humans when excess FA has been inhaled over a long period (Soffritti et al., 2002). In addition, oral administration of FA in drinking water at concentrations of 33.3 mM and 166.5 mM can cause hyperplasia, hyperkeratosis, erosion and/or ulcers in the alimentary system of rats (Conaway et al., 1996). Exposure to FA vapor also induces myocardical ischemia (Rety&Marin, 1957), while rats infused with 0.12 mM FA suffer cardiovascular attacks (Strubelt et al., 1990).

Studies on the relationship between exogenous FA and the immune system have indicated that exposure to FA promotes the response of cultured mast cells (Fujimaki et al., 1992), activates the immune system, and increases related antibodies in human sera (Patterson et al., 1986; Thrasher et al., 1990).

An overload of exogenous FA induces damage to the nervous system including changes in neurofilament proteins and demyelination (Perna et al., 2001). When exposed to FA, rats perform poorly at finding food in a maze, compared with controls (Pitten et al., 2000) and are also deficient in locomotor and explorative behavior (Malek et al., 2003). Hsp70 is upregulated in neonatal rats which have inhaled 0.40 mM FA for 30 days, leading to damage to the hippocampus, such as the loss of neurons and granule cells, and reduction in the volume of the dentate gyrus (DG) and cornu ammonis (CA) (Sarsilmaz et al., 2003; Petushok et al., 2005; Aslan et al., 2006; Sarsilmaz et al., 2007). Inhalation of FA at a concentration of 13.3 μ M alters the expression of mouse genes, such as N-methyl-D-aspartate (NMDA) receptor subunits (NR2A and NR2B), cyclic AMP responsive element-binding protein (CREB)-1, CREB-2, FosB/ Δ FosB, dopamine receptor subtypes (D1 and D2) and transient receptor potential vanilloid receptor (TRPV1), affecting synaptic plasticity (Ahmed et al., 2007; Lu et al., 2008). Epidemiological studies on the exposure of pathologists, embalmers, and chemical workers, have shown that increased hours of exposure to FA per day are associated with reduced performance in memory, equilibrium, and dexterity, and

even result in damage to the central nervous system (Kilburn et al., 1987; Perna et al., 2001; Yu et al., 2007) and headache, eye irritation and asthma-like symptoms of wheezing and bronchoconstriction (Conaway et al., 1996).

1.3 Endogenous formaldehyde

1.3.1 Source of endogenous formaldehyde

FA is present in living organisms in three states, that is, the free-state, or reversibly or irreversibly bound to macromolecules (Zhiqian Tong, 2008). FA is involved in one-carbon metabolism and plays a role in physiological processes (Abeles R.H., 1992). Increased levels of endogenous FA are believed to be a potential risk factor for health and an indicator of either pathological processes, malnutrition or environmental contamination (Kalasz, 2003).

There are several sources of endogenous FA in living organisms, arising from enzymatic or nonenzymatic reactions (Zhiqian Tong, 2008). In plants, FA is produced as a byproduct of photosynthesis and is present at a level of 0.5-1.0 mM. After its generation, the aldehyde moiety immediately combines with L-arginine to form N(G)-trihydroxymethyl-L-arginine (TriHMA) through a series of enzymic reactions (Trezl et al., 1998).

In animals, oxidative deamination is considered to be the major source of endogenous FA (Yu et al., 2003a). One important enzyme involved in FA generation by deamination is semicarbazide-sensitive amine oxidase (SSAO). SSAO, a copper-containing enzyme, is located primarily in cardiovascular smooth muscle, cartilage and other organs including the lung, liver, duodenum, kidney, and adrenal gland, and is circulated in the blood (Morrison et al., 1996; Yu et al., 1997; Mahy et al., 2001). The main substrates of SSAO are aromatic and aliphatic amines, which are deaminated into ammonia, hydrogen peroxide and FA as final products (Mahy et al., 2001; Conklin et al., 2004). In addition, monoamine oxidase (MAO) A and B, enzymes which have a similar function of that of SSAO, also generate FA (Ramonet et al., 2003). Adrenaline, whose excretion is enhanced by stress, is deaminated by monoamine oxidase (MAO) A and forms methylamine as a product. This product can be further deaminated by SSAO, yielding FA in vivo (Yu et al., 1997). In the rat liver microsome, N-nitrosodimethylamine can be metabolized into FA via oxidative deamination (Keefer et al., 1990).

FA is also generated in the demethylation step of methionine-homocysteine cycles. For example, demethylation of S-adenosyl-L-methionine, a methyl donor in enzymatic transmethylation reactions, generates FA (Kalasz, 2003). In addition, Generation of FA can also be achieved via demethylation of other substrates. For example, liver mitochondria produce FA by the oxidation of sarcosine methyl carbons (Abeles&Mackenzie, 1956). In normal and leukemic human leukocytes, N⁵-methyltetrahydrofolate undergoes an oxidative reaction catalyzed by a reductase to form N⁵,N¹⁰-methylenetetrahydrofolate which then spontaneously releases FA. Moreover, production of FA is higher in the lymphocytes of chronic lymphocytic leukemia patients than in those of healthy individuals (Thorndike&Beck, 1977).

Histone demethylation is another way of generating FA in vivo (Kalasz, 2003; Ehrlich, 2009). Histone demethylases catalyze the removal of histone methyl groups at lysine or arginine residues, generating FA as a byproduct (Fang&Tian, 2007). There are two kinds of histone demethylases, namely lysine specific demethylase 1 (LSD 1) and Jumonji C (JmjC) domain family proteins (Fang&Tian, 2007). LSD1, a nuclear homolog of amine oxidases, functions as

a histone demethylase and transcriptional co-repressor, catalyzing the demethylation of histone H3 at lysine 4 and the generation of FA (Shi et al., 2004). JHDM1 (JmjC domain-containing histone demethylase 1), an enzyme which plays a role in the demethylation of histone H3 at lysine 36, also releases FA as a product (Zhang et al., 2006).

Demethylation of DNA and RNA is also believed to involve FA generation. Fat mass and obesity associated enzyme (FTO), a Fe(II)-and-2-oxoglutarate-dependent oxygenase, is able to demethylate 3-methylthymine in single-stranded DNA, leading to the formation of FA (Gerken et al., 2007). In addition, human ABH2 and ABH3, homologues of *E. coli* AlkB, are non-Fe(II)-mediated oxidative demethylases. They are involved in catalysis, releasing the methyl carbon of DNA and RNA as FA (He et al., 2009).

Microsomal cytochrome P-450 dependent oxidation of xenobiotics such as drugs, is another demethylation reaction which results in the production of endogenous FA. In addition, endogenous FA can also come from food, such as milk, ham, sausage, potato, grape and cauliflower (Trezl et al., 1997).

1.3.2 Analysis of endogenous formaldehyde

A variety of methods have been established for the analysis of endogenous FA. According with the universal principle, measurements by different methods result in different values for the concentration of endogenous FA. Dimedone-¹⁴C, a reagent for radiometric analysis, can be used to estimate the FA concentration in human blood and urine. Using this method, FA levels in blood and urine have been shown to vary between 0.01-0.02 mM and 0.08-0.13 mM, respectively (Szarvas et al., 1986). Gas chromatography (GC) has been used to compare the concentration of FA in the expired air of tumor-bearing mice (1.43-2.98 μ M) and control mice (0.77-1.01 μ M) (Shibamoto et al., 1997). The concentration of FA in urine from healthy individuals ranges from 1.89-4.81 μ M, as determined by gas chromatography (Takigawa et al., 2007). The level of FA in the rat brain is reported to be 0.33-30.0 μ M, as determined by GC-MS (P. Maboudou, 2002). Using selected ion flow tube mass spectrometry (SIFT-MS), the mean values of urine FA concentrations in patients with prostate cancer and bladder cancer was shown to be 0.83 μ M and 2.83 μ M, respectively, compared with 0.37 μ M in healthy controls (Smith et al., 1999). In another study, preconcentration of the body fluid samples rendered FA more detectable by SIFT-MS. FA concentrations in Hela S3 cervical cancer, K562 leukemia and MCF-7 breast cancer cell lines range from 1.5 to 4.0 μ M (Bierbaum et al., 2001). The use of high performance liquid chromatography (HPLC) combined with an electrochemical procedure is an established method for the measurement of FA in vivo (Su et al., 2011). An adduct between FA and other reagents can be selectively separated by HPLC, and then quantified by an electrochemical approach. Using this method, the FA concentration of rabbit urine was found to be about 18 nM and that of mouse liver, kidney and brain tissues to be 63, 51 and 11 nmol/g tissue, respectively (Yu et al., 2003a). Another method to determine FA in blood samples by HPLC utilizes a fluorescence assay. Derivatization of human plasma with ampicillin leads to a fluorescent adduct which can be measured with a fluorescence spectrophotometer. The FA level in human blood as determined by Fluo-HPLC is 0.04 mM (Luo et al., 2001). Thin-layer chromatography can also be used to estimate the level of FA (Kalasz, 2003). In addition, the FA level in solid tissues such as teeth can be measured by HPLC-OPLC-MS. Results show an increase in FA level in carietic teeth in comparison to healthy teeth (Rozylo et al., 2000).

1.3.3 Degradation of endogenous formaldehyde

The degradation of endogenous FA mainly occurs via enzymatic catalysis. Aldehyde dehydrogenase I, and III (ADH I, ADH III), and alcohol dehydrogenase II (ALDH II) are three important enzymes involved in these reactions (Iborra et al., 1992; Zhiqian Tong, 2008). There are five classes (I-V) of alcohol dehydrogenase located in human tissues. Transcripts of class II (ALDH II) are abundant in the liver, but low in the stomach, pancreas and small intestine (Estonius et al., 1996). It has been reported that ADH III is also present in the human brain, being distributed mainly in the dendrites and cytoplasm of cerebellar Purkinje cells. The location of ADH III in the brain contributes to defending the brain against degeneration (Mori et al., 2000; Olson et al., 2003). In addition, S-formylglutathione hydrolase, glyoxalase II and catalase also function in the degradation of FA (Zhiqian Tong, 2008).

2. In vitro investigations

2.1 Low concentrations of formaldehyde promote Tau aggregation

Neuronal Tau, an important microtubule-associated protein, functions in facilitating the assembly of microtubules and maintaining their stability (Weingarten et al., 1975; Drechsel et al., 1992). Aberrant modifications of Tau protein, such as hyperphosphorylation which induces misfolding and aggregation, lead to microtubule system damage and subsequent disturbance of axonal transport and neuronal morphogenesis (Cuenda et al., 2005; Terwel et al., 2008). Hyperphosphorylated Tau is the major component of paired helical filaments (PHFs) in neurofibrillary tangles (NFTs), an important characteristic of tauopathies which include neurodegenerative conditions such as Alzheimer's disease (Goedert et al., 1996; Hardy, 2006).

The focus of research in our group is on the relationship between FA-mediated impairments and age-related dementia. Our results showed that native Tau exhibited globules with a diameter of 9 ± 2 nm, while FA-treated Tau had a significantly increased diameter of 18 ± 3 nm in the presence of 18.0 mM FA. The increased diameter of Tau globules was dependent on FA concentration. The rapid onset of aggregation (within 10 min) was followed by a marked increase in particle size. These results were confirmed by SDS-PAGE, where an increase in the polymer bands and a decrease in the monomer bands was seen with increasing FA concentration or time. In addition, light-scattering data (at 480 nm) showed that the intensity of FA-treated Tau was considerably enhanced compared with the control, further confirming that FA induced the aggregation of Tau (Nie et al., 2005). Thus, we proposed a putative mechanism of FA-induced Tau aggregation. A formaldehyde molecule first interacts with a Tau monomer. As additional FA molecules interact with other Tau monomers, the FA molecules polymerise, finally resulting in the cross-linking of the Tau molecules (Nie et al., 2007).

The wormlike conformation of Tau at room temperature, as determined by circular dichroism (CD), is reported to have a minimal content of secondary structures (Schweers et al., 1994). It was observed that the probability of the collision of KI with Tyr residues became smaller after the aggregation of Tau, and suggesting that Tyr residues may shift to the interior of the Tau molecule during aggregation, leading to the lower availability of Tyr residues for KI. The fluorescence of 8-Anilino-1-naphthalene-sulfonic acid (ANS), a

fluorescent probe which binds to the hydrophobic regions of proteins, was enhanced as Tau was treated with FA, demonstrating the formation of a hydrophobic core during Tau aggregation. Protease rapidly cleaved native Tau to produce fragments with an apparent molecular mass of 36-37 kDa. However, no digested fragments were observed after Tau was incubated with FA, suggesting that the cleavage sites recognized by the protease were buried in the aggregates of Tau (Nie et al., 2005). In conclusion, these reports indicate that FA is able to induce neuronal Tau to misfold, resulting in aggregation and conformational changes.

2.2 Tau aggregates induced by formaldehyde are molten globules

Though protein misfolding is believed to induce cellular metabolic dysfunction and even cell death, the mechanism of this phenomenon remains unclear. A number of pathological mechanisms have been proposed and can be divided into two categories: one which suggests that the products of protein misfolding initiate the “death pathway” (Lipton&Nakamura, 2009; Gu et al., 2010), and the other which proposes that “aspecific amyloid ion channels” composed of misfolded proteins cause damage to membrane permeability and result in the disturbance of ion metabolism (Lin et al., 2001; Lal et al., 2005; Lal et al., 2007). ThT fluorescence ($\lambda_{\text{ex}} = 450 \text{ nm}$) and Congo Red staining (measured by light absorbance at 400 nm - 600 nm) increased markedly, indicating that Tau aggregates had features of amyloid-like protein. Using atomic force microscopy, we observed that FA-induced Tau aggregates appeared to have a “pore-like” structure with a diameter of $8.94 \pm 1.62 \text{ nm}$ in the middle of the aggregate. In addition, when Tau was incubated without FA, it formed fibril-like or amorphous aggregates instead of “pore-like” aggregates. It should be noted that these “pore-like” aggregates were observed at a high FA concentration under the experimental conditions, and whether they exist in vivo need to be further investigated. This might provide insights into the mechanism of tauopathies which result from protein misfolding and aggregation (Naqvi et al., 2010).

2.3 Formaldehyde-induced aggregation interferes with Tau’s protection of DNA

Many studies have shown that Tau protein is located in axons and neuronal soma and has important functions in the microtubule system as a microtubule-associated protein (Binder et al., 1985). Recent findings have demonstrated that Tau is also present in the nucleus (Loomis et al., 1990; Johnson&Davis, 1999) and functions in the protection of DNA (Galas et al., 2011). Heat stress and oxidative stress induce the accumulation of nonphosphorylated Tau in the nuclei of neurons. These nuclear Tau accumulations display an enhanced capacity for interacting with DNA and protect DNA from damage by stress (Galas et al., 2011). Other studies have reported that nuclear Tau binds preferentially to polynucleotides of ~13 bp in length, while further research has indicated that Tau binds to the minor groove of the DNA double helix and that both its proline-rich domain (PRD) and microtubule-binding domain (MTBD) contribute to its interaction with DNA. This binding protects DNA from both digestion by DNase I and damage by peroxidation (Wei et al., 2008).

Electrophoretic mobility shift assays (EMSA) showed that native Tau retarded the mobility of DNA while no retardation was observed when DNA was incubated with either Tau aggregates induced by FA, or with BSA, indicating that Tau binding to DNA is suppressed

by aggregation. That is, the aggregation of Tau induced by FA inhibits its ability to bind to DNA and may result in the loss of Tau's protection of DNA (Hua&He, 2002; Lu et al., 2011). These observations suggest a novel mechanism of cell death during the pathological progress of tauopathies, such as neurodegenerative conditions.

3. In vivo investigations

3.1 Formaldehyde-induced aggregation of Tau can be observed in vivo

FA induced significant aggregates in cells. Tau-1 (an antibody which recognizes Tau protein) signals confirmed that Tau forms aggregates in the presence of FA. In addition, apoptosis of HEK 293 cells transfected with *tau* increased, while cells transfected with a control vector showed no increase in apoptosis (Nie et al., 2007). In another study we found that FA-induced Tau aggregates promoted apoptosis in both the SH-SY5Y cell line and rat hippocampal primary cells (Nie et al., 2006). These reports indicate that Tau aggregates induced by FA lead to apoptosis.

3.2 Formaldehyde treated mice perform abnormally in spatial reference memory tests

Test of mice by Morris water maze showed that the latency to platform of FA-treated mice was twice as long as controls and the length of time they spent in the target quadrant was nearly half that of controls, indicating that significant impairment of spatial reference memory function occurred when mice were treated with FA for 30 days. When resveratrol (0.5 mM), a natural FA scavenger, was administrated to mice along with FA, the FA-induced effects on learning memory were attenuated. That is, FA-administrated mice act in abnormal performance in spatial reference memory tests.

3.3 Excess endogenous formaldehyde is positively correlated with memory decline and cognitive impairment in animals

Since FA can pass through the blood brain barrier (Grönvall et al, 1998; Shcherbakova et al., 1986), it is necessary to detect the level of FA in the brain in order to determine the influence of FA on the central nervous system (CNS). The FA level in the brain of three types of Alzheimer's disease mouse model, 5 month-old senescence accelerated mice (SAMP8), 3 month-old APP/PS1-transgenic mice, and 6-month old APP-transgenic mice, was estimated by Fluo-HPLC to be about 0.33, 0.46 and 0.56 mM/g, respectively. Concentrations of FA in the brains of these AD models were all significantly higher than their respective controls (Tong et al., 2011). In addition, FA levels in the brains of rats were inversely correlated to their behavioral performance in the Morris water maze (Tong et al., 2011). In summary, endogenous FA concentrations in the brains of AD animal models (SAMP8, APP/PS1 and APP transgenic mice) are significantly higher than their respective controls, and excess endogenous FA can induce memory decline and cognitive impairment in animals.

In addition, β -amyloid deposits, the other main characteristic of AD in addition to neurofibrillary tangles, increase on treatment with FA in vitro (Yu et al., 2006) and excess endogenous FA also promotes the deposition of A β (Yu et al., 2007). Elevated levels of FA have also been detected in patients with multiple sclerosis (Khokhlov et al., 1989).

4. Clinical trials

4.1 Urine formaldehyde levels in AD patients are correlated with the degree of dementia

The study on the relationship between urine FA level and the degree of dementia showed that the percentage of patients with mild cognitive impairment (MCI), and medium and severe dementia in which concentrations of urine FA increased compared with that of age-matched healthy controls was 42% (21/50), 82.05% (32/39) and 88.46% (46/52), respectively (Tong et al., 2011) (Weishan Wang, 2010).

These results indicate that cognitive impairments of patients with age-related dementia are probably related to endogenous FA levels, and suggest that measuring urine FA levels together with mini mental state examination (MMSE) may be a useful non-invasive method for the investigation and diagnosis of age-related dementia.

4.2 High levels of formaldehyde are observed in the brains of AD patients

In addition to urine samples, we also measured the FA levels in homogenates from autopsy hippocampus tissues of AD patients by Fluo-HPLC. We found significant increases in the FA concentrations in AD patients (about 0.081 mM/g; n = 4) compared with normal controls (about 0.047 mM/g; n = 4) (Tong et al., 2011), indicating once again that endogenous FA level in AD patients is correlated with the progress of dementia.

5. Formaldehyde stress

Though the concept of “formaldehyde stress” has been mentioned in studies on *Methylobacterium extorquens* AMI (Miller, 2009) and tuberculosis (Bottiglioni&Sturani, 1955), the definition of “formaldehyde stress” in neural cells was first proposed by our group. Abnormal accumulation of endogenous FA can cause abnormal modifications and misfolding of proteins, resulting in neural cell responses such as DNA damage, and even cell death (Figure 1). These may lead to dysfunction of related nervous system and cognitive impairments (He et al., 2010).

5.1 Endogenous formaldehyde overload can induce chronic impairment and sporadic age-related dementia

Studies indicate that the level of endogenous FA in humans is maintained homeostatically (around 0.083 mM in urine), but increases with aging. Endogenous FA levels in AD patients and AD mouse models are notably higher than their respective normal controls. Stress induced by excess endogenous FA leads to chronic impairments of the CNS and may contribute to age-related dementia (He et al., 2010; Hao et al., 2011).

5.2 Putative mechanism of formaldehyde accumulation and formaldehyde stress

As mentioned above, generation and degradation of endogenous FA mainly depends on enzymatic reactions. With aging, dysfunction of these enzymes may cause abnormalities in the formaldehyde cycle and aberrant enzymatic production of FA from endogenous and exogenous substrates results in the accumulation of FA, leading to stress and subsequent

pathogenic neurodegeneration (Morrison et al., 1996; Tyihak et al., 1998; Kamino et al., 2000; Yu et al., 2003b; Unzeta et al., 2005; Unzeta et al., 2007). Other factors in aging can also produce excess endogenous FA. Decreased levels of glutathione (GSH) induced by oxidative stress lead to higher levels of endogenous FA (Tyihak et al., 1998; Ling et al., 2006). β -amyloid peptide, a biomarker of Alzheimer's disease, is believed to enhance ROS production and cause a decline in the activity of ALDH2, leading to the production of excess FA (Ohta&Ohsawa, 2006). APOE ϵ 4, considered to be a risk factor of AD, can act synergistically with the deficiency of ALDH 2 to result in accumulation of FA (Ohta et al., 2008). In addition, lipid peroxidation (LPO) (Lemeshko&Nikitchenko Iu, 1982b, a; Dahl&Hadley, 1983; Fokin et al., 1989; Halliwell&Chirico, 1993), abuse of drugs (for example, nicotine and cocaine) (Dahl&Hadley, 1983), and air pollutants (for example, endrin) (Bagchi et al., 1992) can also lead to the accumulation of FA. Polymorphisms in aldehyde dehydrogenase may be correlated with the metabolism and accumulation of FA (Thomasson et al., 1991; Wang et al., 2002; Li Hai-han 2006; Yang et al., 2008). *Adh3* mutant mice are more vulnerable to FA, indicating that dysfunction of this gene is related to abnormal metabolism of FA and causes severe toxicity (Duester et al., 1999).

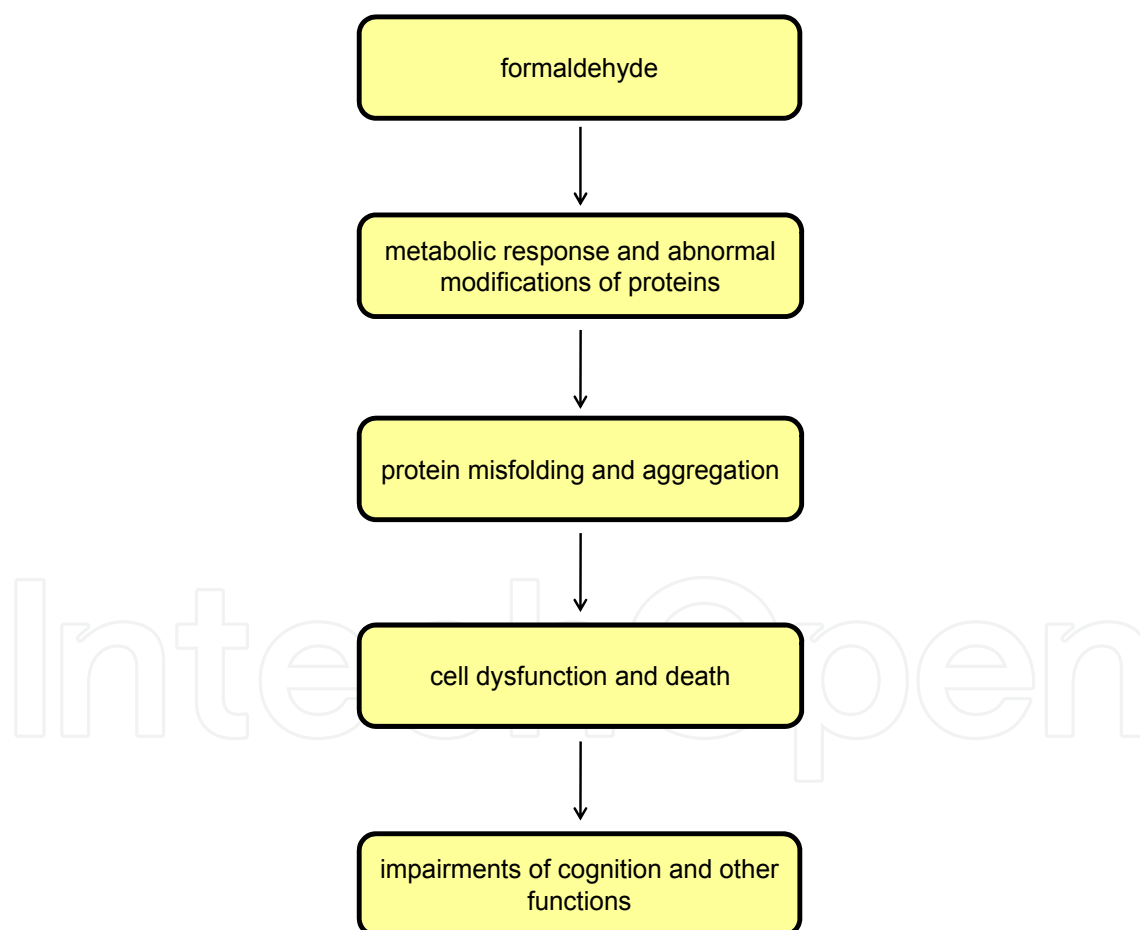


Fig. 1. A putative scheme for formaldehyde stress. Formaldehyde stress is defined as a cellular response which occurs when there is an overload of formaldehyde. Under formaldehyde stress, abnormal modifications of proteins, such as hydroxymethylation and hyperphosphorylation, is present, leading to protein misfolding and aggregation and even to cell death.

6. Perspective

Since FA level is related to cognitive impairments, eliminating excess endogenous FA may become a novel therapy for age-related dementia. Trans-resveratrol (trans-3,5,4'-trihydroxystilbene, Res), a phytoalexin, is a natural ingredient in grapes and various medicinal plants. Res, as a scavenger of FA, can eliminate excess FA and may prevent cells from formaldehyde stress (Tyihak et al., 1998; Marcsek et al., 2007; Marambaud et al., 2008; Gibson et al., 2009; Sun et al., 2010). Antioxidant drugs, such as vitamin E and C, can inhibit lipid peroxidation and the resultant generation of FA (Arlt S, 2001; Yu et al., 2007; Jin-xia., 2009). In addition, iron chelators can enhance the ability of cells to resist the cytotoxicity of FA (O'Brien et al., 2001).

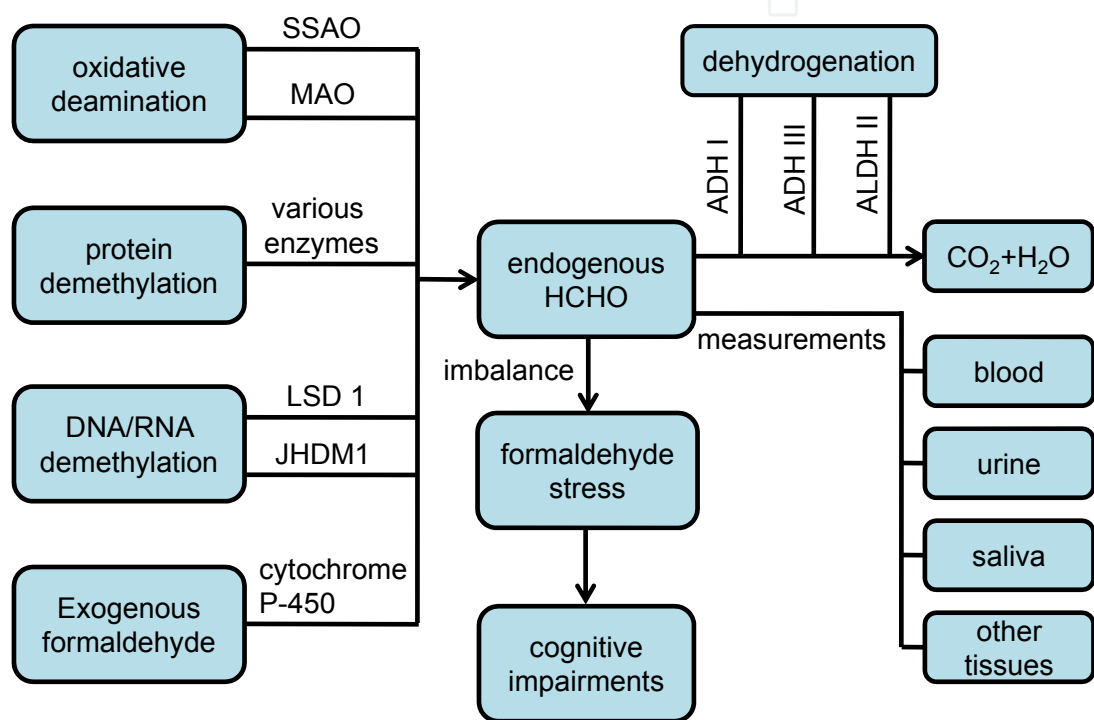


Fig. 2. Formaldehyde stress and the metabolism of endogenous formaldehyde. Endogenous formaldehyde is generated by a variety of enzymes via deamination, demethylation and other reactions. Aldehyde (alcohol) dehydrogenases are the main enzymes involved in the degradation of formaldehyde. Endogenous formaldehyde exists in all tissues such as blood, urine, saliva and brain. Aberrant metabolism causes an increase in endogenous formaldehyde and induces formaldehyde stress, resulting in the dysfunction of organs, especially cognitive impairments.

In summary, excess endogenous FA leads to “formaldehyde stress”, which causes aberrant modification of protein and subsequent protein misfolding and aggregation. The aggregated protein loses its normal physiological function and initiates cell death, organ dysfunction, cognitive impairments and even age-related dementia. Elimination of excess endogenous FA may provide an approach to the therapy of dementia (Figure 2).

Though the relationship between endogenous FA and neurodegeneration has recently received considerable attention, the molecular events involved in FA-induced dementia are still unclear. Since the pathological factors in neurodegenerative diseases including

Alzheimer's disease are complicated and synergistic, further studies should be carried out to reveal the mechanism by which FA contributes to the induction of age-related dementia.

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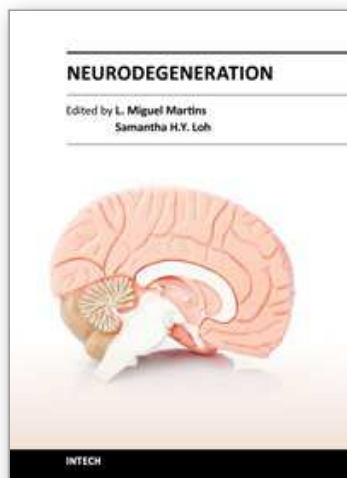
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Currently, the human population is on a collision course for a social and economic burden. As a consequence of changing demographics and an increase in human individuals over the age of 60, age-related neurodegenerative disorders are likely to become more prevalent. It is therefore essential to increase our understanding of such neurodegenerative disorders in order to be more pro-active in managing these diseases processes. The focus of this book is to provide a snapshot of recent advancements in the understanding of basic biological processes that modulate the onset and progression of neurodegenerative processes. This is tackled at the molecular, cellular and whole organism level. We hope that some of the recent discoveries outlined in this book will help to better define the basic biological mechanisms behind neurodegenerative processes and, in the long term, help in the development of novel therapeutic approaches.

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