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Formaldehyde stress

HE RongQiao[1*], LU Jing[1,2] & MIAO JunYe[1,2]

[1]*State Key Laboratory of Brain and Cognitive Sciences, Institute of Biophysics, Chinese Academy of Sciences, Beijing 100101, China;*
[2]*Graduate University of Chinese Academy of Sciences, Beijing 100049, China*

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Formaldehyde, one of the most toxic organic compounds, is produced and processed in human cells. The level of human endogenous formaldehyde is maintained at a low concentration (0.01–0.08 mmol L^{-1} in blood) under physiological conditions, but the concentration increases during ageing (over 65 years old). Clinical trials have shown that urine formaldehyde concentrations are significantly different between elderly Alzheimer's patients (n=91) and normal elderly volunteers (n=38) (P<0.001). Abnormally high levels of intrinsic formaldehyde lead to dysfunction in cognition such as learning decline and memory loss. Excess extracellular and intracellular formaldehyde could induce metabolic response and abnormal modifications of cellular proteins such as hydroxymethylation and hyperphosphorylation, protein misfolding, nuclear translocation and even cell death. This cellular response called formaldehyde stress is dependent upon the concentration of formaldehyde. Chronic impairments of the brain resulted from formaldehyde stress could be one of the mechanisms involved in the process of senile dementia during ageing.

formaldehyde, Alzheimer's disease, senile dementia, stress, cognition, impairment, hyperphosphorylation

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Familial Alzheimer's disease is a very rare autosomal dominant disease with early onset. In contrast with familial disease, sporadic Alzheimer's disease is very common [1]. Even though senile dementia has been widely studied [2–6], the exact cause of the sporadic form of the disease remains unknown. Epidemiological research has shown that exogenous formaldehyde exposure leads to human cognitive decline, and is associated with neurofilament and cytoskeleton disruptions and axonal demyelination [7–9]. Though stress induced by exogenous formaldehyde on *Methylobacterium* [10], rats [11] and humans [12] has been reported, the cellular mechanism needs to be investigated. Here, we show the role of excess endogenous formaldehyde as a putative risk factor that is related to sporadic senile dementia. Formaldehyde stress occurs in a cell when either extracellular or intracellular formaldehyde is elevated abnormally.

1 Formaldehyde commonly exists in exogenous and endogenous human environments

Formaldehyde may have been produced by photochemical reactions in the Earth's primitive atmosphere at a time when it consisted mainly of molecular nitrogen, water vapor, carbon dioxide, and trace amounts of molecular hydrogen and carbon monoxide [13]. According to the *Toxicological Review of Formaldehyde Inhalation Assessment* by the Environmental Protection Agency USA (June 18, 2010), formaldehyde is present in a wide variety of products including some plywood adhesives, abrasive materials, insulation, insecticides and embalming fluids. The major sources of anthropogenic emissions of formaldehyde are motor vehicle exhaust, power plants, petroleum refineries, coking operations, incinerating, wood burning, and tobacco smoke. Formaldehyde is used in industry to manufacture building materials and numerous household products and consumer products. To a certain extent, humans live in an environ-

*Corresponding author (email: rongqiaohe@gmail.com)

Table 1 Generation and degradation of intrinsic formaldehyde

Formaldehyde generation	Localization	Formaldehyde degradation	Localization
Lysine specific demethylase 1 (LSD1)	Nucleus [14]	Alcohol dehydrogenase I (ADH1)	Cytoplasm [23]
Serine hydroxymethyl transferase (SHMT)	Cytoplasm mitochondria [15]	Alcohol dehydrogenase III (ADH3 or ADH5)	Cytoplasm nucleus [24]
Semicarbazide-sensitive amine oxidase (SSAO)	Cytoplasm, membrane [16]	Formaldehyde dehydrogenase (FDH/ADHIII)	Cytoplasm nucleus [23]
Dimethylglycine dehydrogenase (DMGDH)	Mitochondria [17,18]	Aldehyde dehydrogenase 2 (ALDH2)	Mitochondria [23]
AO (alcohol oxidase)	Peroxisome [19]		
Vanillate-O-demethylase (V-O-DMT)	Endoplasmic reticulum [20]		
Lipid peroxidation (LPO)	Membrane lipid [21]		
P450 (CYP2E1)	Mitochondria [22]		

ment containing extrinsic formaldehyde.

As described by Pinto *et al.* [13], reactions of formaldehyde in the primordial aquatic environment would have had implications for the abiotic synthesis of complex organic molecules and the origin of life, i.e., formaldehyde has been involved in living processes from the beginning of life. Pathways which have been found to produce formaldehyde in the human body are shown in Table 1. Organelles within living cells, including the nucleus, cytoplasm, mitochondria, endoplasmic reticulum and membranes, synthesize and release formaldehyde continuously. Formaldehyde metabolism is catalyzed by several enzymes and participates in pathways such as the methylation of DNA [20,25]. Formaldehyde is also produced from the reaction of malondialdehyde with protein [26]. These reports show that humans also live in an environment containing intrinsic formaldehyde.

2 Excess formaldehyde leads to hyper-modification and misfolding of proteins

The half lethal dose (LD_{50}) of formaldehyde in SH-SY5Y cells is 0.1–0.2 mmol L^{-1} [26]. As described previously (Figure 1), formaldehyde causes Tau protein misfolding resulting in amorphous deposits *in vitro*, which can bind to thioflavin T (ThT) and Congo Red [27,28]. One of the major products of the reaction between formaldehyde and the α/ε-amino groups of amino acids is hydroxymethylation. These ThT-positive Tau aggregates induce cellular apoptosis of SH-SY5Y cells and rat hippocampal cells (Figure 2A–D) [29]. Pore-like polymers can be observed after Tau protein is incubated overnight with formaldehyde at 0.5% or higher concentrations (Figure 1E–G) [30], a concentration that is much higher than the LD_{50} for formaldehyde in humans [31]. Further investigation is thus needed to establish whether abnormal elevation of formaldehyde results in pore-like protein aggregations *in vivo*.

Using antibodies (Figure 2), we observed that cellular Tau protein [32] was phosphorylated (Thr-181 and Ser-396) when N2a and SH-Y5Y cells were incubated with formaldehyde (around 0.1 mmol L^{-1}). Furthermore, hyperphosphorylated Tau protein was ThS-positive in the vesicles of

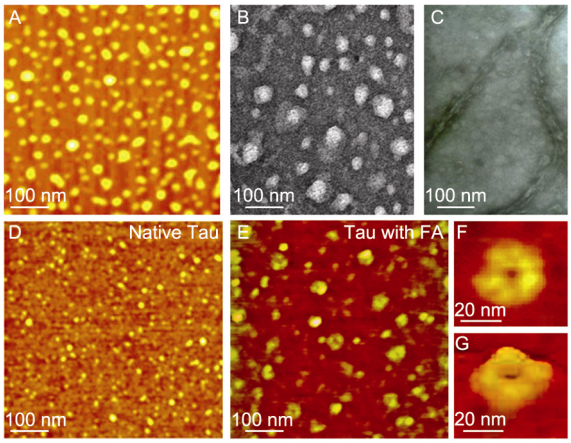

Figure 1 Tau protein in the presence of formaldehyde. Amorphous deposits are observed when Tau protein is incubated with 0.1% formaldehyde for 12 h. A, Atomic force microscopy. B, Electron microscopy. Pore-like aggregates are observed in the presence of 0.5% (or higher concentrations) formaldehyde (E–G). Native Tau (D) and samples incubated without for-maldehyde (C) were employed as controls.

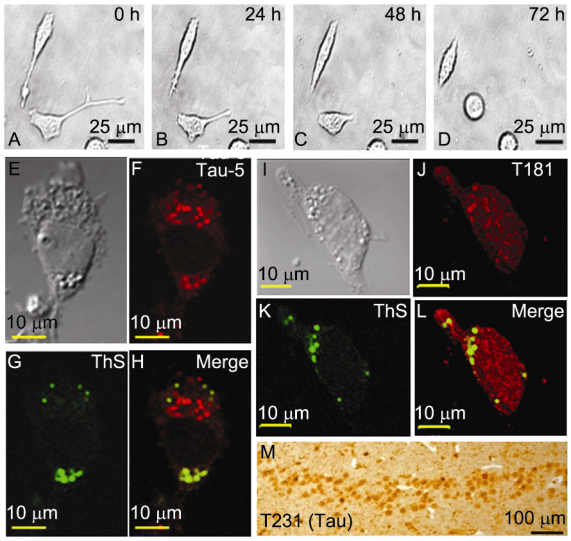

Figure 2 Cells in the presence of formaldehyde and hydroxymethylated Tau. The same SH-SY5Y cells were imaged after incubation with Tau deposits (2 μmol L^{-1}) for 0, 24, 48 or 72 h (A–D). Cells were visualized by inverted contrast microscopy. The neurites became atrophic, and neurons became round in the presence of formaldehyde. Formaldehyde at low concentrations induces phosphorylation, misfolding and aggregation of Tau protein (E–L). Aggregates were ThS-positive. Tau protein was hyperphosphorylated (T231) in the hippocampus of methanol-fed mice (M).

these cells, suggesting misfolding of the modified protein. To confirm that hyperphosphorylation of Tau protein occurs in the presence of formaldehyde, we injected mice intraperitoneally with formaldehyde or fed them with methanol. Hyperphosphorylation of Tau was detected in the hippocampus with a monoclonal antibody (Thr-231). These results suggest that administration of formaldehyde promotes hyperphosphorylation of Tau in neural cells and in the mouse brain.

3 Formaldehyde stress

Abnormal elevation of extrinsic and intrinsic formaldehyde promotes hyperphosphorylation of Tau protein and its aggregation [27,28] and increases amyloid-β deposits [33], accompanied with cellular dysfunction and even apoptosis [28]. Illumina Solexa DNA sequencing exhibited that more than 100 genes were up- or down-regulated in the metabolic pathway in SH-SY5Y cells treated by formaldehyde. Simultaneously, cell shrinkage and rounding can be observed. Thus, formaldehyde stress is properly described as metabolic response and hyper-modifications of protein such as hyperphosphorylation induced by excess concentrations of formaldehyde, followed by protein misfolding and aggregation (Figure 3), accompanied with cell shrinkage and rounding.

Excess formaldehyde can also lead to endoplasmic reticulum stress, leaving proteins unfolded or misfolded in the cytoplasm [27]. The unfolded protein response is activated in response to an accumulation of unfolded or misfolded proteins in the lumen of the endoplasmic reticulum [34]. While formaldehyde stress and endoplasmic reticulum stress can both activate the unfolded protein response, endoplasmic reticulum stress is somewhat different from formaldehyde stress in that hyper-modifications of proteins occur in formaldehyde stress and some modified proteins are transferred into the nucleus.

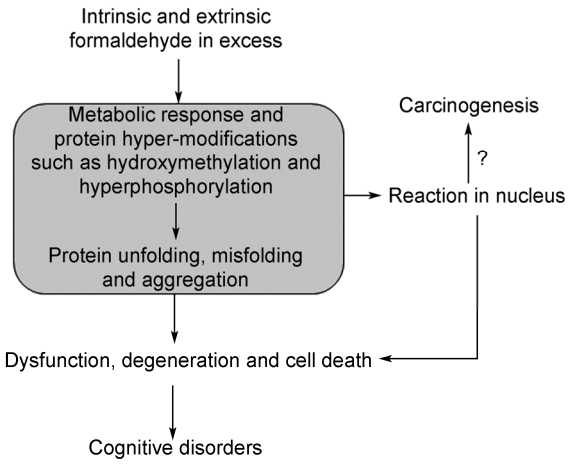

Figure 3 A putative scheme for formaldehyde stress. Formaldehyde stress is best described as hyper-modifications of protein such as hydroxymethylation and hyperphosphorylation in the presence of excess concentrations of formaldehyde, followed by protein unfolding, misfolding and aggregation.

4 Formaldehyde-induced chronic impairment and sporadic senile dementia

According to our clinical studies, the concentration of endogenous formaldehyde tends toward homeostasis (around 0.083 mmol L^{-1} in urine) under physiological conditions, but increases with ageing (Figure 4). The urine formaldehyde concentrations of elderly Alzheimer's patients (n=91) and normal elderly volunteers (n=38) are significantly different (P<0.001) [35,36]. Blood formaldehyde (0.01–0.08 mmol L^{-1}) should be freshly assayed because formaldehyde is very active to react with serum protein. The other lab using HPLC/spectrophotometric procedures has found that the concentration of endogenous formaldehyde in human plasma is 0.017–0.143 mmol L^{-1} [37]. Measurement of saliva formaldehyde is uneasy to correctly perform either on clinic because of elderly people having a low secretion of saliva. Concentrations of formaldehyde in the hippocampus of Alzheimer's patients are significantly higher than those of controls. Formaldehyde concentration in the brain of SAMP8 mouse with cognitive disorders is markedly higher than that in the brain of SAMR1 mouse as the control. Similarly six-month-old APP-transgenic mouse and three-month-old APP/PS1-transgenic mouse have higher formaldehyde concentrations than controls. Abnormally high concentrations of formaldehyde further lead to dysfunction of the hippocampus and cognitive impairment [35]. Chronic impairments of gray matter and white matter in the brain of

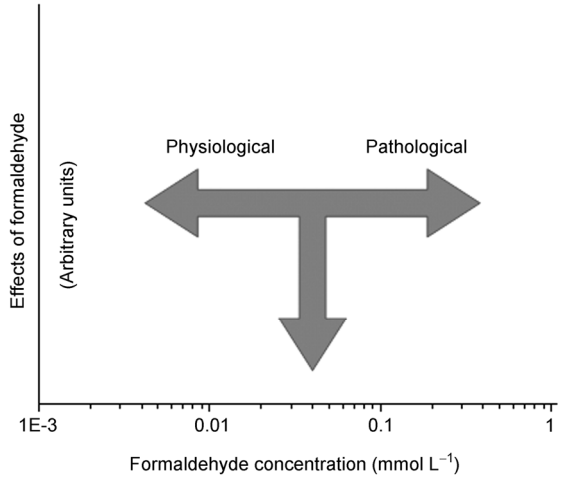

Figure 4 The homeostasis of formaldehyde metabolism *in vivo*. The concentration of endogenous formaldehyde tends to reach equilibrium under normal physiological conditions via synthesis and degradation. We hypothesized that chronic impairment of the central nervous system caused by abnormal elevation of endogenous formaldehyde may be one of the important risk factors for sporadic Alzheimer's disease during ageing.

Alzheimer's patients may result from formaldehyde stress. Illumina Solexa DNA sequencing suggests that some genes related to Alzheimer's disease are strikingly up-regulated in SH-SY5Y cells in the presence of formaldehyde at LD_{50}. That is, abnormal elevation of endogenous formaldehyde may be one of the risk factors which contribute to some cases of sporadic senile dementia.

5 Formaldehyde stress, clinical trials, and drug design

According to our investigations of senior citizens in Beijing, about 20%–40% of senile dementia patients have abnormally elevated urine formaldehyde levels. This suggests that elevated formaldehyde plays a role in senile dementia. The concentration of urine formaldehyde was positively related to cognitive impairments in some patients. Thus, measurement of urine formaldehyde concentration could be used alongside a cognitive questionnaire as a biomarker to support clinical diagnosis.

Further investigations should be carried out using animal models (mice, rats and monkeys) of formaldehyde-induced chronic impairments of the central nervous system. For example, animals could be administered with formaldehyde at certain doses over a relatively long period (1–2 years), and then changes in their brains and cognitive functions could be assessed. The structure and function of formaldehyde metabolic enzymes from Alzheimer's patients and animal models should also be studied. Drugs for decreasing endogenous formaldehyde levels could be designed and evaluated using animal models.

6 Other studies on formaldehyde and Alzheimer's disease

Our previous work has shown that formaldehyde at low concentrations induces Tau protein aggregation in the cytoplasm [27]. Amyloid-β deposits increase in the presence of formaldehyde [33]. Furthermore, disorders in cognitive behaviors occur when animals are exposed to formaldehyde [7,8]. We need to emphasize that not all cases of senile dementia are correlated with an elevation in endogenous formaldehyde or with the dysfunction of formaldehyde metabolism, since the causes of senile dementia are extremely complex. International colleagues have done much work and made great progress in research on Alzheimer's disease [38–42]. At the same time, Chinese researchers have also made important advances in studies on neurodegeneration, including studies on protein misfolding and aggregation [43], hippocampus structure and function [44], β-secretase [45,46], amyloid-beta[47–49], hyperphosphorylation [50–53], and dephosphorylation [54], glycation [55–58], related genes and special RNA [59–61], reactive oxygen species [62], white matter denaturation [63], ubiquitin and proteasome [64], apoptosis [65], plasticity and memory [59,66], chronic inflammation [67], prevention of brain and cognitive function [68,69] as well as clinical studies [70,71]. Although formaldehyde has been shown to play a role in the senile dementia process, much work is still required, especially to elucidate the cellular and molecular events involved in formaldehyde stress.

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