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# Urine Formaldehyde: A Non-Invasive Marker for Alzheimer's Disease?

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**Abstract**

Given the dramatic increase in Alzheimer's disease (AD) cases globally, the identification of a suitable biomarker in easily collectable samples (e.g. plasma, blood, saliva and urine) for diagnosing AD is therefore of utmost importance. Previous studies indicated that excess formaldehyde contributes to Aβ aggregation and Tau hyper phosphorylation, both phenomena directly linked to the progress of AD. Our 7 year's cross-sectional survey showed that morning urine formaldehyde levels were correlated positively with the severe degree of sporadic dementia, suggesting that urine formaldehyde measurement most likely acts as a suitable non-invasive method to support diagnostic purposes.

In this a short review article, we provide a short overview of the animal and clinical studies on the possible mechanisms of exogenous and endogenous factors cause formaldehyde accumulation, which plays a critical role in the pathogenesis of both genetic dementia and sporadic dementia. Urine formaldehyde will be of significant value for the non-invasive diagnosis of cognitive ability in AD, but the more sensitive method for detecting formaldehyde concentrations and a longitudinal (long-term follow-up) study would be required to prove conclusively such a relationship between urine formaldehyde and dementia.

## Urine Formaldehyde Predicts Cognitive Decline in Patients with AD and Stroke

Although Alzheimer's disease (AD) characterized by progressive deterioration in cognitive function was first described over 100 years ago, there is still no suitable biomarker for diagnosing AD in easily collectable samples (e.g. blood plasma, saliva and urine). Stroke patients often suffer from post-stroke cognitive impairment, or even from post-stroke dementia (PSD) [1]. Recently, excess formaldehyde accumulated in the hippocampi has been found in both AD patients and several transgenic AD-like animal models [2]. Surprisingly, excess formaldehyde not only induces the aggregation of Aβ and Tau proteins *in vitro* [3,4] and *in vivo* [5,6], but also leads to vascular damage in patients with stroke, AD [3,7] and PSD [8-10]. These data strongly suggest that accumulated formaldehyde plays a critical role in cognitive decline.

Urine levels of formaldehyde had been found to be inversely correlated with cognition in healthy aging individuals [11] and patients with dementia [2]. A cross-sectional survey for 7 years was carried out in China [12]. The cognitive abilities of the participants (n=577) were assessed by Mini Mental State Examination (MMSE). Morning urine formaldehyde concentrations were measured by high performance liquid chromatography with a fluorescence detector (Fluo-HPLC). The results showed that the optimal threshold of the level of morning urine formaldehyde as a predictive concentration for cognitive impairment was approximately 0.042 mM and formaldehyde levels in healthy control are about 0.02 mM. The findings suggest that morning urine formaldehyde may be a non-invasive marker for AD. More importantly, a non-invasive test which utilizes urine for analysis might potentially help primary-care physicians advice their patients on their long-term prognosis [13].

Remarkably, urine formaldehyde levels were also abnormally elevated in the patients with stroke, PSD [12], post-operative cognitive dysfunction (POCD) [14], multiple sclerosis (MS) [15] and AD [2], when their cognitions were in the process of deterioration. This phenomenon seemly affects that urine formaldehyde acts as a marker in AD. However, these mentioned above diseases have some identifiable clinical characters compared with AD and can be easily diagnosed by clinical doctors. Moreover, the main pathological feature of AD is progressive cognitive decline, urine formaldehyde was found to be inversely correlated with the scores of the Mini-Mental State Examination (MMSE), but neither the Activities of Daily Living (ADL) nor Clinical Dementia Rating (CDR) [2], therefore, urine formaldehyde still could act as a non-invasive marker for AD.

## Exogenous and Endogenous Factors Induce Formaldehyde Accumulation

Although the physiological and pathological functions of endogenous formaldehyde in the brains are not clear until now, formaldehyde is present in the cytoplasm and nucleus of all cells of biological organism [16-19]. Using fluorescence-HPLC, we found that levels of brain formaldehyde are about 0.2~0.4 mM, similar to levels previously reported using gas chromatography/mass spectrometry [20]. Catalysis of the conversion of formaldehyde to formate via class III alcohol dehydrogenase (ADH3) and aldehyde dehydrogenase 2 (ALDH2) known as takes place in all tissues of the human body as a consequence of the regulation of endogenous formaldehyde [20]. Decades of research have established that both exogenous and endogenous factors can induce formaldehyde accumulation and lead to cognitive deficits (Figure 1(a)) [21].

Exogenous factors and Formaldehyde 1) Formaldehyde exposure. Epidemiological investigations indicate that exogenous formaldehyde exposure causes human cognitive decline and is associated with

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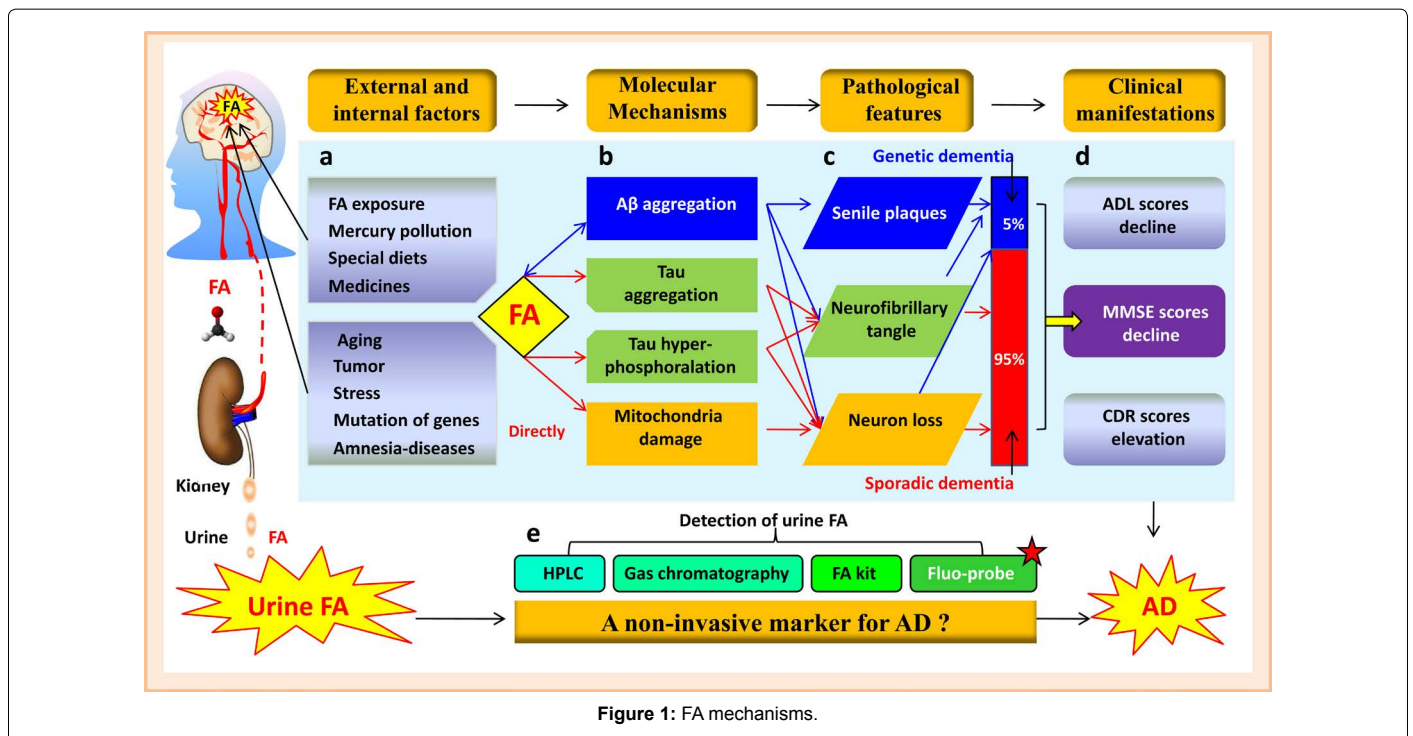
**Figure 1:** FA mechanisms.

neurofilament protein changes and neuron demyelization [22-24]. 2) Mercury pollution. Environmental mercury, which some believe is a pathogenic factor for Alzheimer's disease [25], induces formaldehyde accumulation *in vivo* [26]. 3) Special diets. Formaldehyde participates in the "one-carbon cycle" [17], deficiencies of vitamin B12 or folate in the diet lead to dysfunction of one-carbon metabolism in Alzheimer's patients [27]. 4) Medicines. Endogenous formaldehyde is produced by microsomal cytochrome P-450 and is dependent upon oxidation of xenobiotics, including various drugs and environmental pollutants [28]. For example, abuse of formaldehyde-laced marijuana induces a high occurrence of dysmnesia [29].

Endogenous factors and Formaldehyde 1) Aging. Recent study shows that DNA demethylation leads to formaldehyde generation [30,31]. During aging, a decrease in global hippocampal 5-mC level [32] and an increase in 5hmC content have been observed in hippocampus [33]. Consistently, a wide global DNA demethylation associated with an abnormal high level of formaldehyde was found in autopsy samples from AD patients [34-36]. 2) Tumor. Cancer is known to be related to the occurrence of Alzheimer's disease [37] and cancer cells and tumor tissues release higher levels of formaldehyde than normal cells and tissues [38]. 3) Stress. Formaldehyde is also generated by lipid peroxidation (LPO) and oxidation stress [39,40], which may affect AD pathogenesis. 4) Mutations of formaldehyde metabolism-related genes. Activities of semicarbazide-sensitive amine oxidase (SSAO, a blood formaldehyde-generating enzyme) are elevated in aged rats, as well as in patients suffering from AD [41-43]. Knockout of ALDH2 (a formaldehyde-degrading enzyme) induces memory loss and neurodegenerative disease [44]. In addition, ADH3 (a specific formaldehyde-degrading enzyme [45]) can defense neurodegenerative processes [46-48]. Knockout of ADH3 in Drosophila results in loss of visual memory [49]. 5) Aβ-mediated formaldehyde accumulation. Notably, excess formaldehyde was observed in APP-transgenic mice when memory started to decline on month 6 [50]. Aβ can inhibit alcohol-degrading enzyme activity [51], suggesting that inactivity of

ADH3 leads to formaldehyde accumulation. This working hypothesis needs further investigation. 6) Some diseases associated with amnesia. Through clinical survey, an abnormal high level of formaldehyde has been found in the patients with stroke, PSD, POCD, MS [15] and AD [52]. These exogenous and endogenous factors play roles in formaldehyde accumulation and cognitive decline (Figure1(b)).

## Excess Formaldehyde Promotes the Occurrence of both Genetic and Sporadic Dementia

Substantial clinical surveys of all kinds of dementia have shown that the occurrence of genetic dementia (which is closely related with mutations of APP and/or PSI) is only 5%, but 95% are a variety of pathological factors-mediated sporadic dementia, which is the most common form of AD and is not attributed to genetics (Figures 1(c) and 1(d)). Whether dominantly inherited variants of Alzheimer disease (AD) and 'sporadic' forms exhibit similar pathophysiological and biomarker signatures remains unresolved [53]. However, in our previous studies, there were abnormal high levels of formaldehyde in patients with these two kinds of dementia [2] and indeed caused memory deficits in mice and dementia in patients.

Formaldehyde and genetic dementia Increases in brain formaldehyde observed occurred at a similar time (from as early as 3 months of age) to the development of abnormal LTP levels in APP/PS1 transgenic mice [54], Interestingly, reduced LTP parallels plaque appearance and increased Aβ levels and abnormal short-term memory (working memory). In APP-transgenic mice, brain formaldehyde also increased at the early stage (6 months old) in which Aβ starts to deposit in the brain, and typical senile plaques were detected in the brain of these two types of AD model [54,55]. A potential mechanism is that accumulated formaldehyde induces the aggregation of amyloid (Aβ) [3,4], as well as the hyperphosphorylation and aggregation of Tau proteins [5]. In return, Aβ can inhibit the activity of alcohol dehydrogenase [52], suggesting that inactivity of ADH3 leads to

formaldehyde accumulation. In addition, a natural formaldehyde capturer [56], resveratrol, provides effective defence against cancer and neurodegenerative disease including AD [57,58]. Recent research has also shown that dietary supplementation with resveratrol reduces senile plaque (SP) pathology in a APP/PS1-transgenic model of AD [55]. These data indicate that excessive formaldehyde is involved in the pathogenesis of genetic dementia.

Formaldehyde and sporadic dementia our clinical survey showed that urine formaldehyde concentrations were markedly elevated in patients with sporadic dementia (not including genetic dementia) than healthy age-matched control [12]. The same results also were observed in the different kinds of animal models with sporadic dementia. For example, an abnormal high level of formaldehyde accumulates in the brains of SAMP8 mice (a sporadic age-related dementia model) and in the autopsy hippocampi from patients with genetic dementia-AD [2]. Another sporadic model of AD has been established by only knockout of formaldehyde-degrading enzyme gene-ALDH2 [59]. These ALDH2-/- mice are considered as an age-related model of cognitive deficits [60] and associated with AD-like pathologies including Tau hyper-phosphorylation, brain atrophy and cognitive deficits [60]. Individuals carrying ALDH2 variants are vulnerable to neural damage and to develop AD [61]. These data indicate that excess formaldehyde can induce sporadic dementia.

Furthermore, we found that injection of formaldehyde into hippocampus can mimic the damage effects of excess formaldehyde, which directly induces neurons death and memory deficits [62]. Similarly, exposure of rats to gaseous formaldehyde causes formaldehyde accumulation [63], decreases the number of hippocampal neurons [64] and leads to memory decline [65]. These diverse lines of evidence indicate that excess formaldehyde in the brains leads to genetic dementia and sporadic dementia (Figure 1(b)).

## More Sensitive Method for Detecting Urine Formaldehyde is required for Clinical Diagnosis

Interestingly, urine formaldehyde rather than blood formaldehyde is more suitable for reflecting the metabolism of endogenous formaldehyde *in vivo* [12]. As active formaldehyde is prone to react with serum proteins, blood formaldehyde (about 0.08 mM) are more stable than urine formaldehyde levels from healthy adult (about 0.02 mM). Previous study indicated that blood have an the equilibrium of reactions involving the one-carbon sources, therefore, blood formaldehyde concentrations are often relatively stable [66]. It's worth noting that urine contains very little residual proteins [12]. To rule out of the urine proteins interfering with the fluorescence signal of the formaldehyde-derivative by using Fluo-HPLC, a high speed of centrifugation of all urine samples (8,000 xg) was necessary for the precipitation of urine proteins from the supernatants [12].

Using this method of Fluo-HPLC, urine formaldehyde levels were detected in the range from 0.009 to 0.565 mM, which is consistent with previously reported data [67]. Although these existing approaches provide accurate and ultrasensitive assays for formaldehyde detection in biological samples, several disadvantages such as expense, sophisticated experimental procedures, and noxious analytical reagents, have limited their practical applications. Therefore, a simple, sensitive and efficient method for determining trace amounts of FA in biological samples is needed. Notably, recent years, some fluorescence probes for detecting formaldehyde have been established (Figure 1(e)) [68-73], these simple and quick methods of Fluo-probes should be used to measure urine formaldehyde in the further study.

## Conclusion

The abnormally accumulation of endogenous formaldehyde is important for elucidating the mechanism of cognitive decline in the pathogenesis of genetic dementia and sporadic dementia. Excess formaldehyde enhances Aβ aggregation in genetic dementia, and directly induces neuron loss by damaging mitochondria in sporadic dementia. Tau hyerphosphoralation-induced by formaldehyde may be the common pathway of these two kinds of dementia (Figures 1(a)-1(c)). Evaluation of endogenous formaldehyde in the urine has potential for use as a non-invasive and convenient method for investigation and diagnosis of dementia (Figures 1(d) and 1(e)). Particularly wish to point out that a longitudinal (long-term follow-up) study is very urgently required to prove conclusively such a relationship between urine formaldehyde and dementia. This finding also raises the possibility that urine formaldehyde could be used as a non-invasive marker for the assessment of therapeutics of AD.

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