发布日期：（编辑部填写）

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PIBB 生物化学与生物物理进展

Progress in Biochemistry and Biophysics

内源性甲醛异常蓄积与记忆衰退

童志前　韩婵帅　苗君叶　卢 静　赫荣乔**

（脑与认知国家重点实验室，中国科学院生物物理研究所，北京市 10010）

摘要　本实验室报道了内源性甲醛浓度与认知功能损伤程度之间的关系(Neurobiol. Aging, 2011). 观察到转基因痴呆小鼠(APP、APP/PS1)及衰老加速型(SAMP8)小鼠脑内甲醛浓度较对照组显著升高. 参照痴呆鼠脑内甲醛浓度, 实验人员对正常成年小鼠进行注射, 导致其视觉空间记忆能力减退. 注射甲醛消除剂可以降低老龄大鼠体内甲醛浓度、减少 APP 痴呆模型小鼠脑内的老年斑, 且能观察到记忆功能的改善. 临床观察显示, 老年痴呆患者尿甲醛浓度与认知功能损伤程度之间呈正相关. 甲醛的过量蓄积造成脑慢性损伤, 可能是散发性老年记忆衰退的机制之一.

关键词　痴呆, 甲醛应激, 内源性甲醛, 视觉空间记忆, 记忆衰退

学科分类号　Q5, R74

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*中国博士后基金 20090460047, 973 基金 (2010CB912303;2006CB500703), 国家自然科学基金 NSFC 30970695 和 CAS-KSCX2-YW-R-119, KSCX2-YW-R-256.

**通讯联系人　Tel: 010-64889876, Fax: 010-64853625, E-mail: rongqiaohe@gmail.com

收稿日期：（以本文投稿日期为准）,接受日期：（此项由编辑部填写）

最近研究发现[1], 老龄大鼠在记忆力逐步下降的同时, 其海马甲醛含量随老龄化进程而增加; SAMP8小鼠也有类似情况. 6月龄APP转基因痴呆小鼠脑甲醛浓度也升高, 并伴有记忆能力的下降, 但12月龄时, 其甲醛浓度与对照相近. APP/PS1转基因痴呆小鼠也有类似的表现. 参考痴呆模型鼠脑甲醛浓度, 给正常成年小鼠注射甲醛, 也能观察到其空间记忆能力的下降. 这些结果表明, 脑内特别是海马甲醛的蓄积可能是诱发动物记忆衰退的关键原因之一.

1. 内源性甲醛蓄积与记忆衰退

甲醛是地球形成初期出现的有机分子, 存在于生物体内外. 人血液中甲醛浓度约为0.06~0.08 mmol/L[1], 脑组织内的浓度是血液浓度的2~4倍(0.2~0.3 mmol/L)[3]. Kilburn等与Perna等在动物实验及职业性甲醛暴露人员的研究中发现[4, 5], 气态甲醛暴露可明显引起大鼠记忆能力下降[6], 并伴有海马和皮层神经元的死亡与丢失[7, 8]. 甲醛的吸入能改变大鼠嗅球和海马神经细胞的形态, 海马CA3区CaMKⅡ表达量下降, 也可损害小鼠在水迷宫、六臂放射状水迷宫测试中的能力[9,10, 11, 12].

Khokhlov等发现, 伴有记忆衰退的多发性硬化症(multiple sclerosis)患者, 其血液和脑脊液中甲醛含量明显上升, 而给予甘氨酸对病情有缓解作用[13,14]. 作者研究显示[1], 正常人血甲醛维持在0.06~0.08 mmol/L (n=421), 但随年龄增加有逐渐升高的趋势. 根据本实验室调查结果, 不同年龄健康人(n=236)尿甲醛浓度(约0.06 mmol/L)也有随老龄化进程而增加的趋势. 此外, 尿甲醛浓度(n=141)随痴呆程度的加深而增高, 提示尿甲醛浓度与痴呆的发生呈明显正相关. 数据显示, 分别有42%(21/50)轻度痴呆患者, 82.05%中度痴呆患者和88.46%重度痴呆患者尿甲醛浓度高于正常水平(Figure 1). 痴呆伴高血压(n=21)与单纯性高血压患者相比, 尿甲醛浓度之间具有显著性差异. 痴呆伴糖尿病(n=10)与单纯性糖尿病患者的尿甲醛浓度亦存在显著性差异. 尸检结果表明, 痴呆患者(n=8)海马内甲醛浓度高于正常对照组, 患者皮层甲醛浓度(n=10)也有增高的趋势. 这些结果提示, 老年记忆衰退与内源性甲醛浓度异常升高有关.

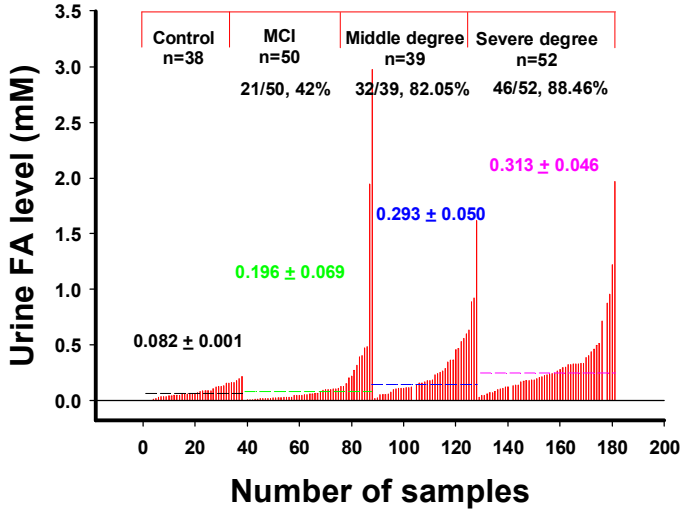

Figure 1. Urine formaldehyde levels of healthy controls and patients with various degree of dementia. Materials and methods were as described in Ref. 1.

3. 体内甲醛蓄积的多重机制

3.1 体内甲醛的来源

除环境中的甲醛污染因素外, 某些食物、药物(butyric acid, AN-7, mitoxantrone 等)是体内甲醛的又一来源[2], 其余的如汞、甲胺、百草枯等也可以通过线粒体细胞色素 P450 的转化作用产生甲醛[15].

酶促反应是体内产生甲醛的主要途径。能够催化底物生成甲醛的酶类主要包括DNA脱甲基化酶、LSD脱甲基化酶、胞浆转甲基化酶、内质网脱甲基化酶、氨基脲敏感的胺类氧化酶、脂类氧化酶、线粒体细胞色素P450酶等[15]. 其中, DNA脱甲基化酶能够催化DNA脱甲基产生甲醛, 这与基因的激活、转录有关[16-19]. 衰老动物[20]和肿瘤细胞[21]的整体DNA处于低甲基化状态, 这也可能是衰老动物和肿瘤细胞内甲醛蓄积的因素之一[2, 22].

3.2 体内甲醛的清除

甲醛降解酶有依赖谷胱甘肽(GSH)甲醛脱氢酶(formaldehyde dehydrogenase, FDH or ADH3), 非依赖谷胱甘肽醇类脱氢酶 1 (alcohol dehydrogenases 1, ADH1)和醛脱氢酶 2 (aldehyde dehydrogenases II, ALDH2). 此外, S-甲基谷胱甘肽脱氢酶(S-formylglutathione hydrolase)、醛酮变位酶(glyoxalase II)、过氧化氢酶(catalase)等也能够降解甲醛[15]. 其中, ADH3 在多种组织器官中存在, 但其活力因不同组织而有差异[23], ADH3 在脑白质的表达高于灰质, 具有抵抗由衰老诱发的神经退行性变[24]. 研究显示, ADH3 过度表达, 可引起果蝇视觉认知功能障碍[25]. ALDH2 体内分布广泛[26], 其活力异常降低时, 可导致记忆能力的下降[27]. 生理条件下, 甲醛主要由依赖 GSH 的 ADH3 进行降解; 当体内甲醛浓度异常升高时, 非依赖 GSH 的 ALDH2 也发挥重要的降解

作用[28].

ADH3 和 ALDH2 的基因具有多态性, 其功能异常与痴呆的发生存在联系[29-31]. ALDH2 基因敲除小鼠记忆力明显下降[27, 32, 33]. APP 被酶切后形成的 amyloid 能抑制线粒体内醇脱氢酶(ADH)的活力, 这也可能是甲醛在 APP 转基因模型鼠中蓄积的原因之一. 作者实验表明, 6 月龄 APP 转基因鼠体内甲醛浓度明显上升[1]. 随着衰老, 体内 GSH 含量逐步减少, 也可能造成 ADH3 酶活力下降, 从而导致机体代谢甲醛的能力降低.

4. 甲醛诱发记忆衰退的神经分子机制

甲醛能自发与蛋白质的α-/ε-氨基发生反应, 导致蛋白质聚积, 活性丧失. 体外实验表明, 低浓度甲醛可以引起神经 Tau 蛋白错误折叠, 令其生物学功能丧失, 并形成细胞毒性聚积物. 甲醛可以透过细胞膜和血脑屏障[34], 引起细胞内 Tau 蛋白的聚积, 导致神经细胞变性死亡[35]. 如果甲醛的浓度升高到一定程度, 便能与胞内更多蛋白质及其他分子进行反应, 造成细胞多方面的损伤. 这可能是“甲醛慢性中枢神经系统损伤”的细胞生物学基础[36-38].

甲醛也能与蛋白的半胱氨酸巯基反应[39-41], 从而封闭蛋白质的侧链巯基[42-44]. 因此, 甲醛可能与 NMDA 受体 NR2B 亚基上的半胱氨酸巯基反应, 影响 NMDA 受体的功能. 美金刚(Memantine, NMDA 受体的拮抗剂)能与 NMDA 受体 NR2B 亚基的半胱氨酸巯基结合[45], 从而对老年痴呆产生一定的疗效. 作者实验表明: 病理浓度的甲醛能够阻断 NMDA 受体, 并抑制海马长时程增强（LTP）的形成, 从而导致大鼠空间学习记忆能力下降. 甲醛浓度异常还可以使皮层编码长时程记忆相关蛋白及其 DNA 甲基化模式被破坏, 诱发海马和皮层神经元死亡, 引起记忆下降(Figure 2).

5. 研究意义和展望

甲醛通过多靶点损伤中枢神经系统, 但其诱发认知功能衰退的机制依然不清楚. 另一方面, 导致体内甲醛蓄积的原因是多方面的, 如环境、药物、肿瘤、老化、基因异常等[2]. 老年痴呆发生发展的病理机制十分复杂, 病因诸多. 从流行病学的角度来分析, 家族遗传性痴呆仅占老年痴呆病例的 3%以下, 而散发性痴呆患者的比例则大于 97%. 临床研究表明, 散发性老年痴呆患者伴有尿甲醛浓度显著升高者占所调查全部病例的 30-40%, 也就是说, 甲醛蓄积造成中枢神经系统慢性损伤，从而诱发认知功能障碍的病例，在老年痴呆患者中占有相当的比例. 因此, 作者假设: 甲醛在脑内蓄积造成的脑慢性进行性损伤, 可能是散发性老年痴呆发病的原因之一[36,47].

蛋白质寡聚化是其功能调节的一种形式[48, 49]. 但是, 蛋白质变性聚集则是神经系统退行性病变过程中的重要表现, 并且是相关领域的研究重点[50, 51]. 低浓度甲醛可以引起神经系统重要蛋白质的错误折叠, 并导致蛋白分子聚集形成神经细胞毒性产物[52, 53]. 一定浓度的白藜芦醇(甲醛清除剂)能降低大鼠体内的甲醛浓度, 对甲醛诱发的记忆衰退有一定治疗效果[1]. 饮水中添加白藜芦醇能减少 APP 转基因痴呆小鼠脑中的老年斑, 提高其空间记忆能力[46]. 这些结果提示，降低内源性甲醛浓度可能成为治疗老年痴呆的新构想.

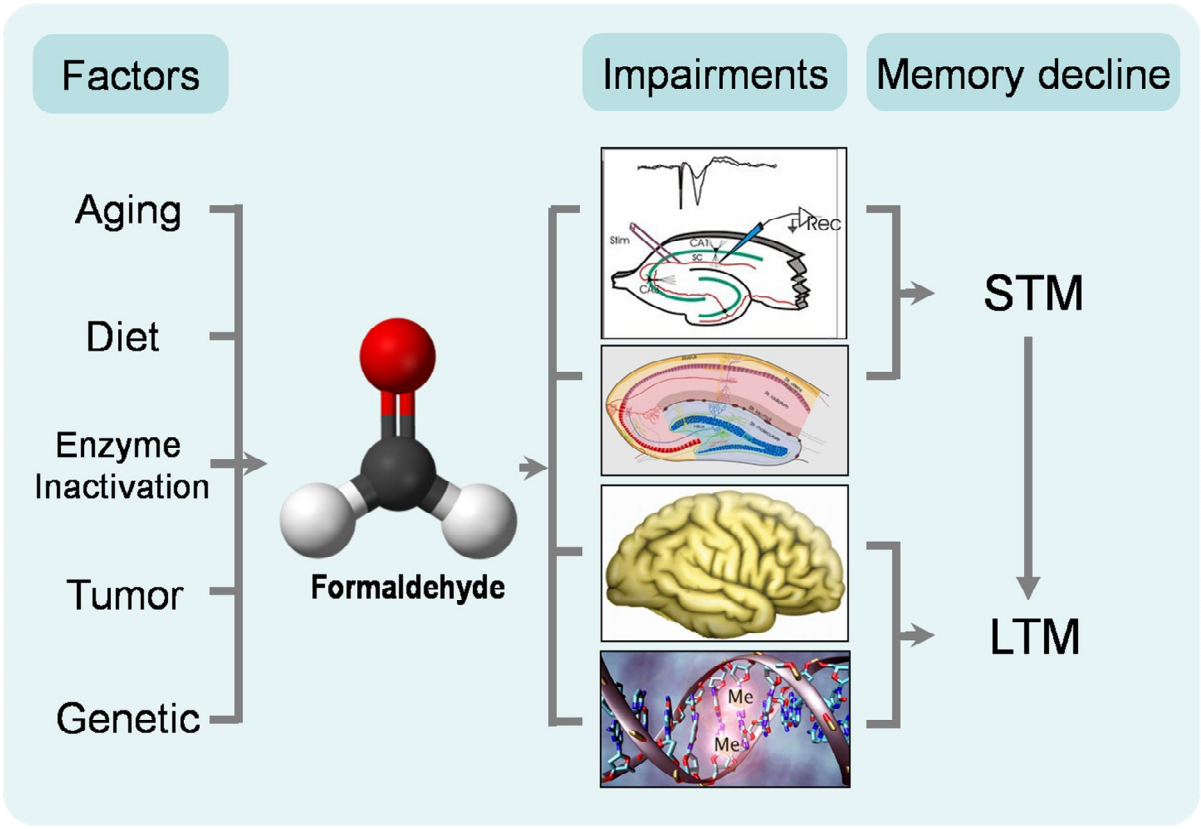

Figure 2. A putative mechanism of formaldehyde-induced memory decline. LTP: long-term potentiation; STM: short-time memory; LTM: long-time memory.

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Excess endogenous formaldehyde induces memory decline

Zhiqian Tong, Chanshuai Han, Junye Miao, Jing Lu, Rongqiao He**

(State Key Laboratory of Brain and Cognitive Sciences, Institute of Biophysics, Chinese Academy of Sciences, Beijing 100101, China.)

Abstract: This review focuses on the relationship between excess endogenous formaldehyde and memory decline, multi-factors inducing formaldehyde abnormal accumulation and cognitive impairments. We discussed elevation of endogenous formaldehyde concentrations in Alzheimer's animal models and clinical patients. Injection with formaldehyde (referred to the detected level in the AD animal models) into normal mice obviously induced spatial memory decline. Aging, genetic factors diet and environmental pollutants led to formaldehyde abnormal accumulation. Formaldehyde scavengers could rescue spatial memory of APP-transgenic mice. These studies addressed that excess formaldehyde-induced damage of brain is one of the critical factors of cognitive impairments of sporadic senile dementia. Scavenging excess formaldehyde may be a novel therapy for Alzheimer's disease.

Key words: senile dementia, formaldehyde stress, endogenous formaldehyde, visual spatial memory, memory decline

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* This work was supported by a grant from Chinese Postdoctoral Fund 20090460047, the 973-Project (2010CB912303; 2006CB500703), the Natural Scientific Foundation of China NSFC 30970695, and CAS-KSCX2-YW-R-119, KSCX2-YW-R-256.

** Corresponding author. Tel: 86-10-64889876, Fax: 86-10-64853625, E-mail: rongqiaohe@gmail.com

Received: Accepted: Available online: