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综 述

内源性甲醛参与调节记忆

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摘 要：甲醛是地球上进化早期阶段最早出现的同时含有C、H、O元素的最简单有机小分子之一，被发现存在于每一个真核细胞中，并参与“一碳代谢”。近期研究表明，内源性甲醛可能作为信号分子参与记忆的形成。电刺激或学习训练后，大鼠脑内甲醛含量瞬时升高，激活*N*-甲基-*D*-天冬氨酸(*N*-methyl-*D*-aspartate, NMDA)受体，促进长时程增强(long-term potentiation, LTP)或空间记忆的形成。相反，降低脑内甲醛含量后，NMDA受体不能被激活，不能形成LTP和短时记忆。在正常老年大鼠和阿尔茨海默病转基因小鼠中，脑内甲醛浓度异常升高，NMDA受体活性受到抑制，空间记忆受损。因此，维持体内生理水平的甲醛浓度对于记忆的形成与储存尤为必要。本文对内源性甲醛在学习和记忆中的生理与病理生理学功能进行了综述。

关键词：内源性甲醛；阿尔茨海默病；NMDA受体；长时程增强；空间记忆
中图分类号：Q42；R742

Endogenous formaldehyde regulates memory

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Abstract: Formaldehyde is one of the simplest organic small molecules containing C, H and O elements in the early stage of earth's evolution; however, it has been found to be existed in every eukaryotic cell and participate in "one carbon metabolism". Recent studies have shown that formaldehyde may act as a signal molecule to regulate memory formation. After electrical stimulation or learning activity, the levels of formaldehyde in rat brains were increased instantly, and *N*-methyl-*D*-aspartate (NMDA) receptor was activated to promote the formation of long-term potentiation (LTP) or spatial memory. On the contrary, after reducing the levels of formaldehyde in the brains, NMDA receptor could not be activated, which was accompanied by the deficits in both LTP and memory. Moreover, in the brains of normal aged rats and APP/PS1 transgenic mice, the concentrations of formaldehyde were abnormally increased, which directly inhibited NMDA receptor activity and impaired spatial memory. This article reviewed the physiological and pathophysiological functions of endogenous formaldehyde in learning and memory.

Key words: endogenous formaldehyde; Alzheimer's disease; *N*-methyl-*D*-aspartate receptor; long-term potentiation; spatial memory

甲醛 (MW = 30) 是地球进化早期最先出现的、最简单的同时含有 C、H、O 元素的有机小分子 [1]。其他的小分子如 NO (MW = 30)、CO (MW = 28)、H_2S (MW = 34) 等伴随生物的进化进入生命体后，能在脑部合成，并作为气态信号分子参与学习和记忆 [2]。目前研究表明，内源性甲醛存在于一切生物的细胞质、细胞核、亚细胞器中 [3]。Heck 等采用气相 - 质谱色谱方法测得动物和人的血液中甲醛浓度一般为 0.08 mmol/L，脑组织内为 0.2~0.4 mmol/L[4]。近年来研究显示，内源性甲醛参与记忆的形成，并与人类许多重大疾病密切相关 [5]。伴随年龄增加而在海马中蓄积的甲醛可能是诱发记忆衰退的关键因素之一 [6]。

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1 外源性甲醛暴露诱发记忆衰退

气态甲醛诱发记忆衰退现象，最早的报道出现在 20 世纪 80 年代的美国。室内装潢甲醛污染、甲醛工业污染等造成工作环境中人员记忆衰退，引起科学家的极大关注 [7, 8]。动物研究显示，甲醛暴露可诱发大鼠记忆下降 [9]。腹腔注射甲醛可致大鼠海马和皮层神经元死亡 [10, 11]。气态甲醛也降低小鼠空间记忆 [12, 13]，显著抑制记忆相关的海马神经递质的合成 [14, 15]。这说明甲醛损坏海马是外源性甲醛暴露诱发空间记忆缺失的主要原因。

2 内源性甲醛蓄积诱发记忆衰退

1989 年，Khokhlov 等发现多发性硬化患者的血液和脑脊液中甲醛浓度异常上升，而甘氨酸能降低甲醛浓度，对病情有缓解作用 [16]。虽然多发性硬化患者常常伴有记忆衰退，但该研究没有对甲醛与记忆的关系进行探讨。

2.1 记忆退化与甲醛蓄积的临床研究证据

Conaway 等检测了 421 例不同年龄健康受试者血液甲醛浓度，发现血液甲醛浓度基本稳定在 0.08 mmol/L，这是因为血液中存在较强的甲醛缓冲体系，但随着年龄的增加，血液甲醛浓度呈现逐渐增加的趋势 [17]。Tong 等研究显示，236 例不同年龄健康受试者尿液中甲醛浓度基本稳定在 0.06 mmol/L，但是随着年龄的增长，呈现显著升高 [18]。Tong 等检测了 141 例不同程度的阿尔茨海默病患者的尿液，发现尿液甲醛浓度随阿尔茨海默病患者的痴呆程度增加而显著增高 [6]。上述研究提示，年龄增长和神经退行性疾病可能导致内源性甲醛含量的升高。

2.2 记忆退化与甲醛蓄积的基础研究证据

衰老是唯一被确定了的诱发阿尔茨海默病的因素。加速老化模型 SAMP8 小鼠、链脲霉素诱发糖尿病模型大鼠造模成功后一个月记忆下降时，海马中甲醛含量也明显增加 [19, 20]。在 APP 单转基因阿尔茨海默病小鼠模型中，6 月龄记忆明显下降时，全脑甲醛浓度上升最明显 [6]。在 APP/PS1 双转基因阿尔茨海默病小鼠模型中，3 月龄记忆明显下降时，全脑甲醛浓度显著上升 [6]。Tong 等的研究提出了关键证据：根据阿尔茨海默病小鼠全脑中甲醛水平，用甲醛 (0.5 mmol/L, i. p.) 处理正常小鼠，Morris 水迷宫实验结果显示小鼠记忆丧失 [6]，这提示海马中蓄积的甲醛可能是记忆衰退的关键原因。

3 体内甲醛蓄积的多重原因

正常脑内的甲醛生理浓度约为 0.3 mmol/L。但随着老年化或阿尔茨海默病发生，脑部蓄积的甲醛逐步达到病理浓度 (约 0.5 mmol/L)[6]，超过体内甲醛降解酶的降解能力，诱发神经元死亡、记忆下降。甲醛的生成和降解酶是调节脑内甲醛平衡的主要途径 (图 1)[5]。

3.1 甲醛降解酶

甲醛降解主要由依赖谷胱甘肽 (glutathione, GSH) 的甲醛脱氢酶 (formaldehyde dehydrogenase，FDH，又称乙醇脱氢酶 3，ADH3)、乙醇脱氢酶 1 (alcohol dehydrogenase 1, ADH1)、不依赖 GSH 的醛类脱氢酶 2 (aldehyde dehydrogenase 2, ALDH2) 进行；其次，S- 甲基 GSH 脱氢酶、醛酮变位酶、过氧化氢酶 (catalase, CAT) 也能降解甲醛。FDH 在脑白质中有强表达，灰质中有中度表达，能抵抗衰老诱发的神经退化 [21]，但它的活力在不同组织中有 12~30 倍的差别，在肝、肾、胃、肠中活力最高，在脑、心、肺、睾丸中活力最低 [22]。ALDH2 降解甲醛的 Km 值为 0.5 mmol/L，比 FDH (Km = 0.3 mmol/L) 的降解能力强 [23]。在生理条件下，甲醛主要由依赖 GSH 的

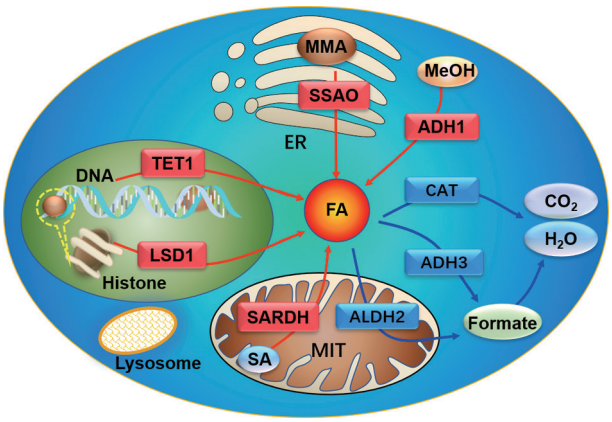

图 1. 内源性甲醛代谢途径

Fig. 1. The multiple metabolic pathways of endogenous formaldehyde. Red arrows: formaldehyde-generating pathways; blue arrows: formaldehyde-degrading pathways. ADH1, alcohol dehydrogenase 1; ADH3, alcohol dehydrogenase 3; ALDH2, aldehyde dehydrogenase 2; LSD1, lysine special demethylase 1; SSAO, semicarbazide-sensitive amine oxidase; SARDH, sarcosine dehydrogenase; SA, sarcosine; TET1, TET methylcytosine dioxygenase 1; CAT, catalase; MMA, monomethylamine; FA, formaldehyde; MeOH, methanol; ER, endoplasmic reticulum; MIT, mitochondria.

ADH3 降解，当体内甲醛浓度过高时，不依赖 GSH 的 ALDH2 发挥更重要的降解作用 [24]。Ohta 等研究显示，当 ALDH2 活力低下时，记忆明显下降 [25]。Murta 等研究显示，当 GSH 耗竭时，CAT 成为 Fischer 大鼠肺部降解甲醛的主要酶 [26]。Tong 等研究显示，抑制 FDH 和 ALDH2 活性可导致大鼠海马甲醛急剧蓄积，引发记忆下降 [18]。

3.2 甲醛生成酶

甲醛主要由下列酶促生成：肌氨酸脱氢酶 (sarcosine dehydrogenase, SARDH)[27]、TET 甲基胞嘧啶双加氧酶 1 (TET methylcytosine dioxygenase 1, TET1)[28, 29]、赖氨酸特异性脱甲基化酶 1 (lysine special demethylase 1, LSD1)[30, 31]、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 [5]。其中，DNA 脱甲基化酶和基因的激活、转录、翻译有关，它脱甲基时产生甲醛 [28, 32–34]。研究显示，DNA 转甲基化酶的抑制剂 5-Aza-2'-deoxycytidine 能促进 DNA 脱甲基，产生甲醛蓄积 [35]。

3.3 食物、药物、环境污染因素

研究显示，香菇、黄瓜和牡蛎等食物能导致体内甲醛上升并超过 0.3 mmol/L，一些药物、环境污染物 (如甲醛污染、离子辐射、汞污染、百草枯、甲胺) 及抗癌药物 (如丁酸、AN-7、mitoxantrone) 等也可以通过线粒体细胞色素 P450 酶转化产生甲醛 [3]。

3.4 老化、老年性疾病因素

植物、动物、人的老化都增加体内甲醛的蓄积 [6,36]。甲醛在多种疾病患者体内显著蓄积，多项研究显示，白血病患者血液 [37]、前列腺癌、膀胱癌患者的尿液 [38]、肺癌患者的呼出气体 [39]、肺癌细胞诱发的骨癌痛模型的骨髓、脊髓 [40]、阿尔茨海默病患者的尿液、海马和阿尔茨海默病的模型动物海马 [6] 中的甲醛浓度升高。

3.5 基因因素

在生理条件下，甲醛主要由依赖 GSH 的 ADH3 降解。ADH3 基因多态现象很常见，与阿尔茨海默病的发生有一定联系 [41, 42]。*ADH3* 基因敲除导致小鼠对甲醛的耐受性明显降低 [43] 和果蝇视觉记忆缺失 [44]。当体内甲醛浓度过高时，不依赖 GSH 的 ALDH2 发挥更重要的降解作用 [24]。研究显示，*ALDH2* 多态现象与阿尔茨海默病的发生密切相关，日本和中国的病例对照研究显示，*ALDH2*2* 等位基因携带者患晚发性阿尔茨海默病的概率较非携带者显著增高，并与载脂蛋白 E 等位基因 4 (*APOE ε4*) 协同作用 [45, 46]。*ALDH2* 基因的突变导致人肝脏降解甲醛能力下降 10% [47]。*ALDH2* 基因敲除的小鼠表现出记忆缺失 [25, 48, 49]。当 GSH 耗竭时，CAT 成为降解甲醛的主要酶。*CAT* 基因在阿尔茨海默病患者人群有多态现象，*CAT* 基因在其启动子区域 (rs1001179) 的 −262 位具有 C/T 多态性，T 启动子变体可以增强该基因的转录活性和酶活力，特别是 TT 纯合子和 CT 杂合子的 CAT 浓度明显升高，但 *CAT* 基因 −262 位 C→T 多态性对阿尔茨海默病患者并未表现出保护作用 [50–52]。CAT 酶活力下降可诱发记忆衰退 [53, 54]。GSH 浓度在衰老大鼠的额叶皮层、纹状体中脑和小脑中明显下降 [55]。脑 GSH 水平低被认为是神经退行性疾病发生的原因之一 [56]。

3.6 表观遗传因素

容易被忽视的另一个甲醛产生途径是：个别基因脱甲基或整体 DNA 的低甲基化，而 DNA 脱甲基可产生甲醛 [28, 32–34]。如在 *APP* 转基因鼠中，*APP* 基因的不断脱甲基，实现过度表达，这伴随着甲醛的产生；同时，Aβ 可抑制 ADH3 的活力，这也可能是甲醛在 *APP* 转基因鼠阿尔茨海默病模型中蓄积的另一原因。该阿尔茨海默病模型鼠 6 月龄时脑内 Aβ 大量产生，并伴随甲醛急剧蓄积 [6]。另外，正常衰老过程中的脑组织全基因组 DNA 甲基化水平降低 [57]，慢性髓性白血病、宫颈癌、前列腺癌和肝癌等癌症组织中的 DNA 也呈低甲基化水平 [58]。DNA 的低甲基化导致甲醛的产生，因此离体培养的肿瘤细胞 DNA 脱甲基诱发甲醛水平上升 3 倍以上 [37]。

4 生理浓度甲醛调控长时程增强(long-term potentiation, LTP)和记忆形成

学习活动能诱发海马甲醛浓度的上升，此时产生的甲醛是 LTP 和空间记忆形成所必需的，提示内源性甲醛可能作为信号分子参与记忆的形成。

4.1 学习活动诱发海马中甲醛产生

近期的研究显示，大鼠进行水迷宫训练后或在体海马 CA1 区给予高频刺激 (200 Hz, 3 trains, 20 pulses) 后，海马甲醛浓度上升至 0.06~0.08 mmol/L[35]。而该浓度甲醛的来源机制很少有报道。有许多酶调节内源性甲醛的产生，如 DNA 脱甲基化酶 [59]、组蛋白脱甲基化酶 (histone demethylases, HDMs)、赖氨酸 - 特异性脱甲基化酶 (lysine-specific demethylase 1, LSD1)[60] 和线粒体细胞色素 P450 酶 [3]。Guo 等研究显示，电刺激能够诱发海马约 3% 的整体 DNA 脱

甲基化，位于神经元核内的 DNA 脱甲基化酶是外界刺激后神经元内甲醛浓度上升的关键酶 [61]。在 DNA 脱甲基化酶或其他相关酶的介导下，DNA 的脱甲基可导致甲醛的产生 [32, 59, 62, 63]。DNA 脱甲基药物 5-Aza-2'-deoxycytidine 可以抑制 DNA 甲基转移酶的活性，诱发整体 DNA 脱甲基化、甲醛的产生 [35, 64]。以上研究表明，学习活动的刺激可诱发海马神经元 DNA 脱甲基，导致甲醛的产生。

4.2 内源性甲醛调控LTP和记忆

Tong 等研究显示，0.08 mmol/L 的甲醛能增强 *N*-甲基 -*D*- 天冬氨酸 (*N*-methyl-*D*-aspartate, NMDA) 受体活力，促进海马 LTP 的形成 [18]。而向侧脑室注射 FDH，大鼠海马 LTP 明显受抑，并伴随大鼠的空间记忆缺失 [35]。相反，在 32 月龄的老年大鼠海马中测得的甲醛浓度是 0.5 mmol/L，而向健康大鼠侧脑室注射 0.5 mmol/L 甲醛可显著抑制海马 LTP 的形成。同样，侧脑室注射甲醛降解酶的抑制剂如琥珀酸 (ADH3 抑制剂) 或 daidzin (ALDH2 抑制剂)，可引起海马中的甲醛急剧蓄积，并抑制海马 LTP 的形成 [18]。以上研究表明，内源性甲醛浓度对 LTP 和空间记忆的形成有重要作用。

5 病理浓度甲醛破坏短期记忆

伴随年龄增加，海马中甲醛逐步蓄积。而过多的甲醛引发的损害作用包括：阻断 NMDA 受体，破坏海马 LTP 形成；降低记忆相关蛋白 NR2B、突触蛋白 SNAP25、VAMP2 的表达，减弱突触功能；诱发储存短期记忆的海马神经元死亡；降低海马内去甲肾上腺素水平 [65]；减少脑内褪黑素，引起海马强烈的氧化应激 [66]，以上多重作用可导致短期记忆下降或学习困难。

5.1 甲醛阻断NMDA受体从而破坏LTP形成

NMDA 受体广泛分布于中枢神经系统。一般认为 NRl 和 NR2 亚基组装在一起，形成 NRl/NR2 的聚合体。两个亚单位共同围绕成离子通道，对学习和记忆起决定性作用 [67]。研究显示，敲除 NMDA 受体的 *NR2B* 基因后小鼠记忆能力下降 [68]，而过表达 NR2B 可使小鼠、大鼠记忆明显增高 [69–71]。老年大鼠脑内 NR2B mRNA 和蛋白表达均明显下调，伴随学习记忆障碍 [72]。Zhao 等研究显示，24 月龄老年 F344 大鼠大脑前扣带皮层中 NR2B 受体的数量显著降低，恐惧记忆无法形成 [73]。而阿尔茨海默病早期患者海马和内嗅皮层 NR2A、NR2B 受体的表达明显下调 [74]。甲醛能通过 NMDA 受体影响谷氨酸的突触传递 [75]，提示 NMDA 受体可能是甲醛作用的靶点。通过氧化还原 NMDA 受体亚基 NR1 和 NR2B 上半胱氨酸组成的二硫键可调节 NMDA 诱发的电流 [76–79]。甲醛能自发地与游离的半胱氨酸发生化学反应 [80–82]，也能与多种蛋白的半胱氨酸残基发生化学反应 [83–85]。病理浓度甲醛可抑制表达在 CHO 细胞上的 NR1/NR2B 介导的内钙上升，抑制大鼠海马 LTP，破坏大鼠空间记忆的形成 [18]。综合上述研究可见，甲醛可能通过化学反应作用于 NMDA 受体，破坏 LTP 形成。

5.2 甲醛降低突触蛋白表达从而减弱突触功能

虽然急性低浓度甲醛暴露后小鼠海马区 NR2A 和 NR2B 表达变化不大 [86]，但是中等浓度甲醛 (3.0 mg/m^3) 吸入后 NR2B 的表达减少 [87]、DNA 甲基转移酶 (DNA methyltransferases, DNMTs) 活力降低 [88]。病理浓度甲醛可通过抑制 DNMTs 活力下调 NR2B 的表达 [18]。阿尔茨海默病患者尸检结果显示海马中甲醛蓄积 [6]，NR2B 表达下调 [72, 74]。SNAP25 和 VAMP2 是表达在海马和皮层中参与学习和记忆的突触蛋白 [89–91]，随年龄增大，这两个突触蛋白的表达减少，伴随记忆下降 [92, 93]。研究显示甲醛暴露可诱发大鼠海马中 SNAP25 和 VAMP2 蛋白表达下调 [94]、空间记忆能力下降 [95]。以上研究表明，甲醛可下调突触蛋白的表达，减弱与学习相关的突触活动。

5.3 甲醛破坏短期记忆形成的脑区——海马

大量的研究表明，甲醛可诱发海马神经元的死亡 [14, 75, 96, 97]。甲醛有较强的水溶性和脂溶性，能透过血脑屏障和细胞膜 [98]，因此甲醛暴露可导致脑中甲醛迅速扩散、渗透，从而升高脑内甲醛浓度 [99]。研究显示，腹腔注射 0.5 mmol/L 甲醛，大鼠脑中甲醛迅速上升，说明甲醛具有相当的渗透性，而天然的甲醛消除剂白藜芦醇可以降低 SAMP8 小鼠海马的甲醛浓度 [18, 65]。同时，病理浓度甲醛能诱发 tau 和 amyloid 蛋白聚集，诱发阿尔茨海默病患者的早期海马神经元死亡 [100, 101]。临床研究显示，海马受损是阿尔茨海默病患者记忆衰退最早的临床特征，这和海马是短期记忆形成和暂时存储的关键部位一致 [102]。以上研究表明，强溶解性的甲醛可以穿透细胞膜，造成海马神经元死亡，破坏记忆的形成与储存。

6 病理浓度甲醛破坏长期记忆

慢性蓄积的病理浓度甲醛可能通过破坏神经元

的轴突髓鞘，阻断了神经核团间通讯、氧化损伤编码蛋白的 DNA (包括 DNA 的甲基化减少)、诱发储存长期记忆的皮层神经元死亡等多重机制，引起长期记忆丢失。

6.1 甲醛破坏神经回路——轴突髓鞘

基础和临床研究都显示，甲醛暴露可导致记忆丢失 [9, 12, 103]。甲醛可诱发神经纤维丝蛋白变性、神经元脱髓鞘 [8]，而神经元脱髓鞘是阿尔茨海默病患者尸检时常常观察到的病理现象 [104–107]，这和多发性硬化疾病相类似 [108, 109]。转基因阿尔茨海默病模型小鼠脑皮层灰质具有多发脱髓鞘现象 [110, 111]。神经元的脱髓鞘导致神经冲动传导受损，使神经核团间通讯受阻，从而引起记忆的提取失败，而深部脑刺激 (deep brain stimulation, DBS) 能暂时恢复部分神经核团间联系，使记忆涌现 [112–115]。甲醛消除剂白藜芦醇有保护神经元髓鞘的作用 [116, 117]。以上研究提示，消除脑内过多的甲醛，保护神经元髓鞘，对于阻止记忆损伤可能具有可行性。

6.2 甲醛破坏记忆信息编码器——DNA

长期记忆的形成，需要 DNA 脱甲基、转录、翻译出记忆相关蛋白，其中 DNA 的甲基化是记忆形成的关键步骤 [118–122]。巧合的是，诱发甲醛蓄积和记忆丢失的因素，如老化 [57, 123]、汞污染 [124–126]、杀虫剂 DDT [127]、铅污染 [128] 等，都能显著降低脑 DNA 甲基化水平。同样，对阿尔茨海默病患者尸检结果显示大脑皮层总 DNA 甲基化水平下降 [129–132]。Tong 等研究显示，病理浓度甲醛明显降低 DNA 甲基化水平，并使记忆下降 [35]。阿尔茨海默病患者的血液淋巴细胞、海马和皮层神经元 DNA 受到活性氧攻击导致链断裂，出现 DNA-DNA 和 DNA- 蛋白质交联 [133–135]。吸入病理浓度甲醛会造成大鼠和小鼠鼻黏膜细胞 DNA 的 N^2-hydroxymethyl-dG mono-adducts 和 dG-dG 发生交联，导致 DNA 复制时碱基错配，诱发突变与癌症 [136–139]。以上研究表明，病理浓度的甲醛可破坏已经形成的 DNA 甲基化谱，从而擦去已经形成的长期记忆。

6.3 甲醛破坏长期记忆储存器——皮层

大量研究显示甲醛诱发皮层神经元死亡 [11, 94, 140]。病理浓度甲醛 (0.5 mmol/L) 显著抑制线粒体细胞色素酶活力，降低离体培养的皮层神经元代谢能力 [141]。0.3 mmol/L 甲醛对胶质细胞活力影响不大，但可诱发离体培养的皮层神经元死亡 [142–144]。皮层是记忆储存的地方，临床研究显示，手术切去皮层内侧颞叶系统的患者出现远期记忆丧失等症状 [145, 146]。阿尔茨海默病患者晚期颞叶系统受损严重，出现逆行遗忘、远期记忆丧失 [147–149]。Tong 等研究显示阿

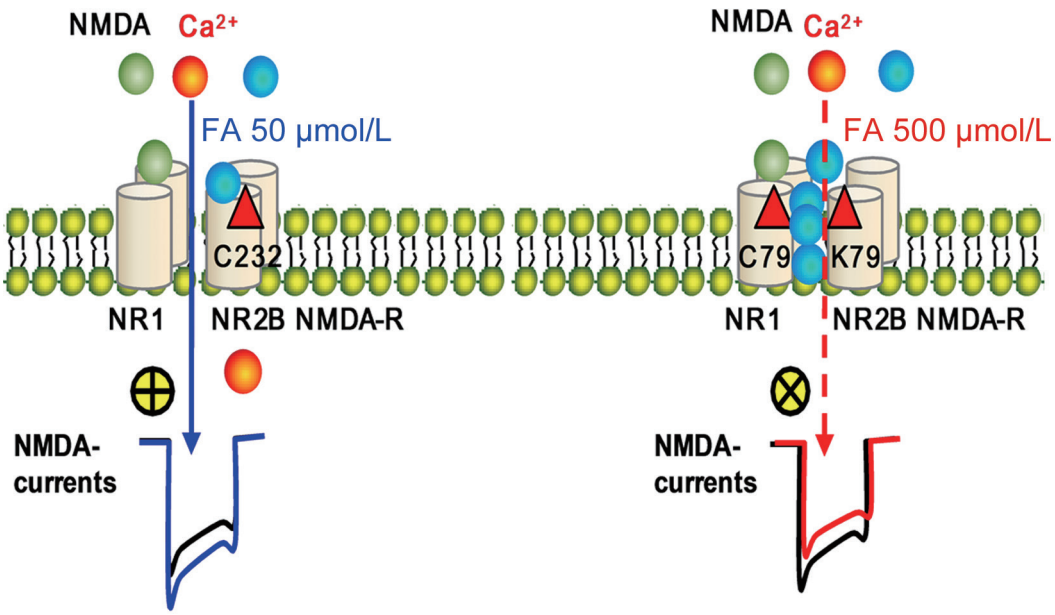

图 2. 不同浓度甲醛对NMDA电流的影响

Fig. 2. Effects of different concentrations of formaldehyde (FA) on *N*-methyl-*D*-aspartic acid (NMDA)-currents. Endogenous FA enhances NMDA-currents by binding to C232 of NR2B, whereas excess FA suppresses NMDA-currents by cross-linking C79 of NR1 and K79 of NR2B. NMDA-R, NMDA receptor. The figure was reproduced from reference [152].

尔茨海默病患者尿液中甲醛浓度随痴呆程度加深而升高[6]。在阿尔茨海默病患者的晚期，体内蓄积过多的甲醛能促进 $A\beta_{42}$ 形成淀粉样聚集的老年斑，同时诱发 tau 蛋白聚集、皮层神经元死亡[100, 101]。

甲醛易与蛋白的半胱氨酸 (cysteine, C)、赖氨酸 (lysine, K) 等位点结合[84, 150]，可诱发蛋白交联，破坏蛋白的结构，影响蛋白的功能[151]。最新研究显示，学习活动诱发的瞬间升高的甲醛可作用于 NR2B 受体的 C232 位点，增强 NMDA 受体的激活，提高记忆；而病理浓度的甲醛可交联 NR1 的 C79 位点和 NR2B 的 K79 位点，关闭 NMDA 受体，减少 NMDA 激活的电流，破坏记忆的形成[152](图 2)。

7 总结和展望

甲醛作为地球上最早出现的有机小分子之一，在机体内参与了生理和病理活动。在生理条件下，学习活动可诱发脑甲醛浓度呈现一定程度瞬时的上升，参与记忆的形成，表明内源性甲醛可调控记忆功能。而当内源性甲醛代谢失衡时，如中风 [氨基脲敏感型胺氧化酶 (semicarbazide-sensitive amine oxidase, SSAO) 活力增强]、衰老 (甲醛降解酶活力降低)、癌症 (DNA 脱甲基增强)、糖尿病 (*ALDH2* 基因突变) 及神经退行性疾病发生时，脑内甲醛浓度异常升高，破坏记忆的形成和提取。这些研究结果提示我们，对于阿尔茨海默病及其他认知障碍相关疾病，可能通过调整脑内甲醛的代谢来改善记忆丢失等症状，这给相关疾病治疗药物的研发提供了新思路、新策略。

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