·基础研究·

# 阿司匹林对阿尔茨海默病模型鼠学习记忆能力及海马区炎性因子表达水平的影响

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【摘 要】 **目的** 观察阿司匹林(Asp)对阿尔茨海默病(AD)模型大鼠空间学习记忆能力及海马区炎性因子白细胞介素1β(IL-1β)、肿瘤坏死因子α(TNF-α)、IL-4及IL-10表达水平的影响,探讨Asp在AD防治中的潜在抗炎作用。**方法** 40只大鼠随机分为4组:对照组、AD模型组、低剂量Asp干预组和高剂量Asp干预组,10只/组。对照组和AD模型组大鼠自由饮用双蒸水;低剂量和高剂量组大鼠分别自由饮用1 mg/ml和2 mg/ml的Asp溶液,3周后通过侧脑室注射β淀粉样蛋白($A\beta_{25-35}$)建立AD模型,并继续按前述方法喂养3周,然后通过Morris水迷宫检测大鼠空间学习、记忆能力;酶联免疫吸附实验(ELISA)检测IL-1β、TNF-α、IL-4和IL-10的表达水平。**结果** 与AD模型组相比,高剂量Asp干预组第1、2、3天以及低剂量Asp干预组第3天的逃避潜伏期均显著缩短,差异均具有统计学意义($P<0.05$)。与对照组相比,AD模型组的IL-1β和TNF-α表达水平均显著升高($P<0.001$),而IL-4和IL-10表达水平均显著降低($P<0.05$);低剂量Asp干预组的TNF-α表达水平显著升高($P<0.01$),而IL-4表达水平下降明显($P<0.01$)。与AD模型组比较,高剂量Asp干预组的IL-1β和TNF-α表达水平均显著降低($P<0.01$),而IL-4和IL-10表达水平均显著升高($P<0.05$);低剂量Asp干预组的IL-1β表达水平显著降低($P<0.01$)。**结论** AD模型大鼠通过Asp干预后其空间学习记忆能力提高。Asp可能通过抑制神经小胶质细胞活化,促进抗炎/促炎因子趋于平衡,从而在AD发病过程中发挥保护作用,抑制炎性反应发展。

【关键词】 阿司匹林;阿尔茨海默病;白细胞介素-1β;肿瘤坏死因子-α;白细胞介素-4;白细胞介素-10
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# Effect of aspirin on learning and memory abilities and expression of inflammatory cytokines in hippocampus of Alzheimer's disease rats

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【**Abstract**】 **Objective** To determine the effect of aspirin on the spatial learning and memory abilities and the hippocampal expression of interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), interleukin-4 (IL-4) and interleukin-10 (IL-10) in the rat model of Alzheimer's disease (AD), and to elucidate its potential anti-inflammatory effect in the prevention and treatment of AD. **Methods** A total of 40 SD rats were randomly divided into 4 groups: control group, AD model group, and low- and high-dose aspirin groups ($n=10$). Distilled water was used to feed the rats from the 2 former groups, and 1 mg/ml and 2 mg/ml aspirin were given to the 2 latter groups respectively for 3 weeks. Then the rat model of AD was established by injecting $A\beta_{25-35}$ into the lateral cerebral ventricle, and then all were fed continuously for another 3 weeks. The spatial learning and memory abilities of the rats was tested by Morris water maze. Then the rats were sacrificed and the hippocampal tissues were collected to detect the levels of IL-1β, TNF-α, IL-4 and IL-10 by enzyme linked immunosorbent assay (ELISA). **Results** The mean escape latency was significantly shorter in the high-dose aspirin group at the 1st, 2nd and 3rd days and in the low-dose group at the 3rd day when compared with the model group ($P<0.05$). The expression levels of IL-1β and TNF-α were significantly increased ($P<0.001$), but those of IL-4 and IL-10 were obviously decreased ($P<0.05$) in the model group than the control group. The low-dose group also had notably higher TNF-α and lower IL-4 levels when compared with the control group (both $P<0.01$). High-dose aspirin treatment resulted in obvious decreases of the IL-1β and TNF-α levels ($P<0.01$) and increases of those of IL-4 and IL-10 ($P<0.05$) than the AD group. However, low dose

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of aspirin only decreased IL-1β level ($P < 0.01$). **Conclusion** Aspirin intervention promotes the spatial learning and memory abilities in AD rats. It exerts protective effect in the pathogenesis of AD and inhibits the development of inflammatory response through inhibiting glial activation and improving the balance of pro- and anti-inflammatory cytokines.

【**Key words**】 aspirin; Alzheimer's disease; interleukin-1β; tumor necrosis factor-α; interleukin-4; interleukin-10

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2015年,全球约有阿尔茨海默病(Alzheimer's disease,AD)患者4680万,而到2050年,预估每85人中将有1人遭受AD影响[1]。AD是最常见的老年痴呆类型,在其进程中β淀粉样蛋白(amyloid β-protein,Aβ)斑块和神经纤维缠结诱发的神经炎性反应可能是其主要病理学变化,而Aβ异常聚集可能是AD发病机制的启动因子,神经纤维缠结则可能更多地参与了AD的进展过程,神经炎性反应可引起促炎因子白细胞介素-1β(interleukin 1β,IL-1β)、IL-6、肿瘤坏死因子-α(tumor necrosis factor α,TNF-α)等生成增加,而抗炎因子IL-4、IL-10、转化生长因子β(transforming growth factor,TGF-β)等不足也可能促进神经炎性反应[2],神经炎性反应在AD早期进程中可能发挥了核心作用[3]。神经炎性反应被认为是大脑内先天免疫系统被激活,其主要功能就是保护中枢神经系统对抗感染性损害、外伤或疾病[4]。小神经细胞激活在启动炎性级联反应、释放炎性因子和活性氧、引起tau蛋白异常磷酸化和神经纤维缠结形成、促进神经细胞破坏和凋亡等方面都发挥重要作用;而小神经胶质细胞还可通过吞噬作用清除脑内Aβ多肽,因此,通过抗炎药物抑制炎性反应、保护神经胶质细胞,可改善神经病理学变化中的潜在可能[5]。

有临床研究表明长期服用阿司匹林(aspirin,Asp)的人群AD发病率较未服用者降低[6]。因此,本研究通过对SD大鼠侧脑室注射$A\beta_{25-35}$建立AD动物模型[7],探讨Asp干预对AD模型大鼠空间学习能力及海马组织中抗/促炎因子IL-1β、TNF-α、IL-4及IL-10表达水平的影响,以期能为AD的防治提供部分实验依据。

## 1 材料与方法

### 1.1 实验动物

清洁级雄性SD大鼠40只,鼠龄11~12周,体质量290~320 g,购自第二军医大学实验动物中心。标准环境下饲养:温度(23.0±0.5)℃,湿度(50.0±0.5)%,自然光线(昼夜比12∶12),自由进食水。

### 1.2 试剂和仪器

$A\beta_{25-35}$和Asp均购自美国Sigma公司;大鼠IL-1β、TNF-α、IL-4、IL-10定量酶联免疫吸附实验(enzyme linked immunosorbent assay,ELISA)试剂盒均由欣博盛公司提供。Morris水迷宫实验视频分析系统(北京众实迪创公司);脑立体定向仪(Stoelting公司,美国);5 μl微量注射器(杭州镇海玻璃仪器厂)。

### 1.3 方法

1.3.1 $A\beta_{25-35}$溶液和Asp液配制 将$A\beta_{25-35}$溶于无菌生理盐水(10 mmol/L),密封后置于37℃,5%$CO_2$恒温箱内孵育3 d,老化备用。将Asp颗粒研磨后加入双蒸水,振荡溶解配制成浓度为1 mg/ml和2 mg/ml的溶液。

1.3.2 分组及处理方法 40只大鼠随机分为4组:对照组、AD模型组、低剂量Asp干预组和高剂量Asp干预组,10只/组。对照组和AD模型组大鼠自由饮用双蒸水;低剂量和高剂量组大鼠分别自由饮用1 mg/ml、2 mg/ml的Asp溶液。3周后侧脑室注射$A\beta_{25-35}$,并继续上述方法喂养3周。各组大鼠均自由进食。

1.3.3 AD大鼠模型建立 用2%戊巴比妥钠腹腔麻醉(40 mg/kg)大鼠,固定于脑立体定向仪上,剪去头顶部毛发,聚维酮碘消毒后切开皮肤,参照包新民的《大鼠脑立体定位图》,选择右侧脑室为注射靶区,于前囟向后1.0 mm、中线向右旁开1.8 mm处,用三棱针钻开颅骨,暴露硬脑膜,再用微量注射器自脑表面垂直进针3.9 mm,将10 mmol/L的$A\beta_{25-35}$溶液5 μl缓慢注入侧脑室(5 min),留针2 min,缓慢撤针(5 min),牙科粉覆盖颅骨开口,消毒后缝合皮肤切口,肌注4万单位青霉素钠预防感染;对照组注入等体积无菌生理盐水。

1.3.4 Morris水迷宫行为学测定 各组大鼠于第6周结束后进行Morris水迷宫实验(隐匿平台获得实验),测试程序为定位航行试验:历时5 d,前2 d为训练适应期,后3 d记录实验成绩,将受试大鼠按顺时针方向依次由E、S、W、N 4个点入水,面向池壁放入水中,记录寻找和爬上平台所需的时间(逃避

潜伏期)。如果大鼠在120 s内找到平台,记录其实际逃避潜伏期;如果在120 s仍未找到平台,则由实验者将其引上平台并停留20 s,逃避潜伏期记录为120 s。

1.3.5 海马组织提取及IL-1β、TNF-α、IL-4和IL-10定量ELISA测定 用2%戊巴比妥钠腹腔麻醉(40 mg/kg)大鼠,快速去头并取出完整大脑,在冰盒上去除皮层组织,暴露并分离出海马,保存到2.0 ml冷冻管的液氮中。大鼠海马匀浆离心后取上清,根据ELISA试剂盒说明书所示方法,使用酶标仪测定样品在450 nm的吸光度(absorbance,A),根据标准品结果绘制标准曲线,直线回归分析得出其回归方程。将标本的A代入所得方程,可得出相应炎性因子的数值。

### 1.4 统计学处理

采用SPSS18.0软件对数据进行统计分析。计量资料以$\bar{x} \pm s$表示,两组间比较用$t$检验,多组间比较使用单因素(one-way)ANOVA方差分析。$P<0.05$为差异有统计学意义。

## 2 结 果

### 2.1 各组大鼠Morris水迷宫逃避潜伏期比较

第1天Morris水迷宫实验结果显示,AD模型组逃避潜伏期较对照组显著延长,差异具有统计学意义($P<0.001$),表明造模成功。与对照组相比,AD模型组和低剂量Asp干预组第1、2、3天的逃避潜伏期均显著延长,差异均具有统计学意义($P<0.05$)。与AD模型组相比,高剂量Asp干预组第1、2、3天以及低剂量Asp干预组第3天的逃避潜伏期均显著缩短,差异均具有统计学意义($P<0.05$;表1)。

### 2.2 各组大鼠海马组织中促炎因子表达水平比较

与对照组相比,AD模型组的IL-1β和TNF-α表达水平均显著升高($P<0.001$),提示AD模型组海马区炎性反应较显著;低剂量Asp干预组的TNF-α表达水平显著升高($P<0.01$)。与AD模型组比较,高剂量Asp干预组的IL-1β和TNF-α表达水平均显著降低($P<0.01$),低剂量Asp干预组的IL-1β表达水平显著降低($P<0.01$)。高、低剂量Asp干预组间IL-1β和TNF-α的表达水平比较,差异均无统计学意义($P>0.05$;图1)。

### 2.3 各组大鼠海马组织中抗炎因子表达水平比较

与对照组相比,AD模型组的IL-4和IL-10表达水平均显著降低($P<0.05$),提示AD模型组海马区炎性反应显著,低剂量Asp干预组的IL-4表达水平下降明显($P<0.01$)。与AD模型组相比,高剂量Asp干预组的IL-4和IL-10表达水平均显著升高($P<0.05$),提示高剂量Asp干预组大鼠海马区炎性反应受到抑制。高、低剂量Asp干预组间IL-4和IL-10的表达水平比较,差异均无统计学意义($P>0.05$;图2)。

**表1 各组大鼠逃避潜伏期比较**

Table 1 Comparison of escape latency among groups in 3 days ($n=10$, s, $\bar{x} \pm s$)

| Group | 1st day | 2nd day | 3rd day |
|---|---|---|---|
| Control | 30.51±7.68 | 24.12±5.59 | 14.37±2.32 |
| Model | 44.31±7.84*** | 34.81±6.34*** | 21.56±4.06*** |
| Low aspirin | 39.27±10.17* | 33.40±6.37** | 18.10±3.33*# |
| High aspirin | 35.30±4.45# | 28.92±5.59# | 16.68±4.31## |

Compared with control group, *$P<0.05$, **$P<0.01$, ***$P<0.001$; compared with model group, #$P<0.05$, ##$P<0.01$

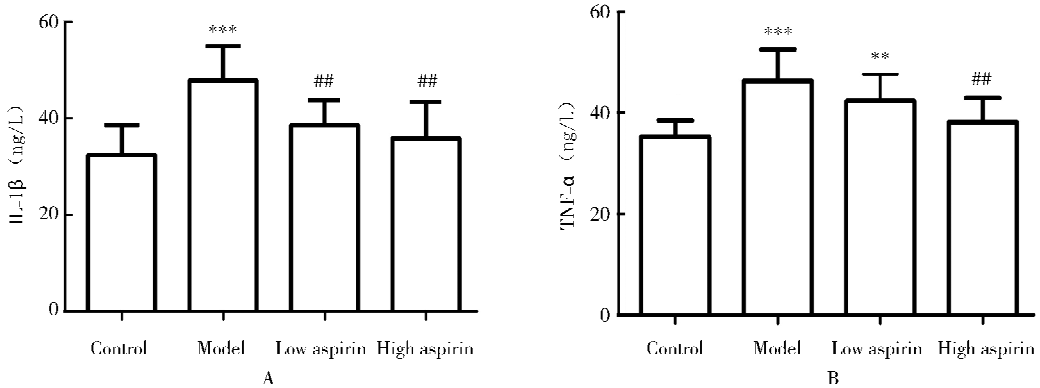



**图1 各组促炎因子表达水平比较**

Figure 1 Comparison of levels of pro-inflammatory cytokines among groups

A: IL-1β; B: TNF-α. IL-1β: interleukin-1β; TNF-α: tumor necrosis factor α. Compared with control group, **$P<0.01$, ***$P<0.001$; compared with model group, ##$P<0.01$

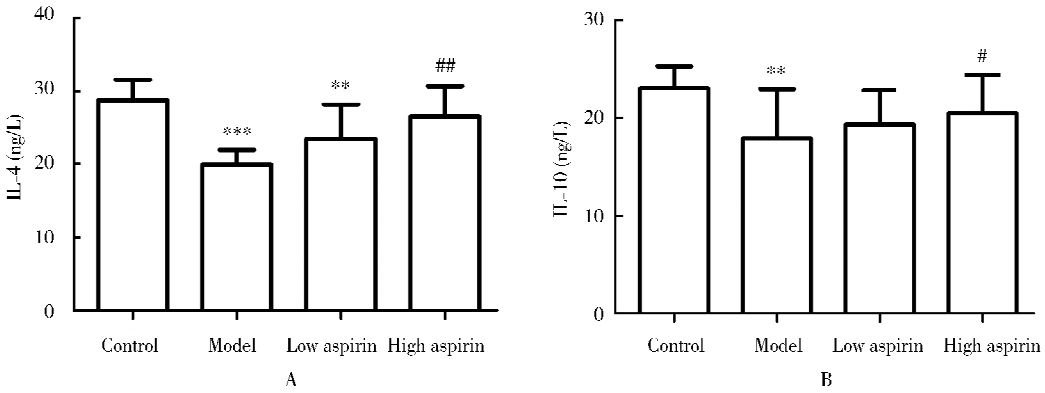



**图2 各组抗炎因子表达水平比较**

Figure 2 Comparison of levels of anti-inflammatory cytokines among groups

A: IL-4; B: IL-10. IL-4: interleukin-4; IL-10: interleukin-10. Compared with control group, $^{**}P<0.01$, $^{***}P<0.001$; compared with model group, $^{\#}P<0.05$, $^{\#\#}P<0.01$

## 3 讨 论

AD是一种多病因、发病机制尚不完全清楚的神经退行性疾病,以认知功能损伤、进行性日常活动能力混乱及神经精神病学症状和行为异常为主要临床特征。Aβ和tau蛋白过度磷酸化分别为细胞外老年斑和细胞内神经纤维缠结的主要成分,这些蛋白的共同特征是生理活性丢失和毒性增加,可促进神经退行性变[8]。尽管其发病机制仍不清楚,但有证据表明神经炎性反应在AD进程中发挥重要作用[9]。且随着AD患者脑内神经炎性反应的不断进展,抗炎反应对促炎因子的刺激持续缺乏,抗炎因子表达水平下降,促炎因子表达水平升高,致使抗炎/促炎因子平衡失调,进一步促进炎性反应的发展。

本实验数据分析结果显示,高剂量Asp干预组大鼠海马组织中IL-1β和TNF-α的表达水平较AD模型组均显著下降,差异均有统计学意义,这与胡毓洪等[10]的研究结果一致;而IL-4和IL-10的表达水平较AD模型组均有不同程度升高,其中高剂量Asp干预组与AD模型组的差异具有统计学意义。IL-4是一种参与调解AD患者脑内神经炎性反应过程并发挥重要作用的多态性抗炎因子。有研究显示IL-4诱导小神经胶质细胞通过促进CD36和Aβ裂解酶基因表达而清除Aβ[11];而用IL-4治疗AD动物模型后,Aβ积累减少,认知功能损害减轻[12]。文献报道[13,14],在IL-4基因表型(-590 C/T和-1098 T/G)中,-590T等位基因被认为具有保护作用,而-1098T在高加索人群中则可能是一个危险因素。IL-10是一种强有力的抗炎因子,在细胞存活和神经元的内稳态中发挥重要作用,可能参与调节IL-1β和IL-6的生成及减少炎性反应[15]。有报道称[3],在预曝光的神经胶质细胞中,IL-10抑制由Aβ或脂多糖诱导的促炎因子生成;而另有研究显示[16,17],在AD小鼠模型中,抗炎细胞因子IL-10通过小神经胶质细胞抑制Aβ清除,加剧认知能力下降。但关于IL-10基因多态性的研究数据显示,-1082GG基因表型(与高IL-10生成相关)和-1082AA基因表型(与低IL-10生成相关)与AD发病率或AD进展的高风险相关[18],但Moraes等[19]认为IL-10 -1082AA和降低AD风险之间相关。这些研究表明探索IL-4和IL-10与AD之间的关系将有助于理解它们在AD进程中发挥的作用,为防治AD提供参考。

Asp是经典的非甾体类抗炎药,其对AD的重要性在于抗炎作用。我们前期实验通过Asp干预$A\beta_{25-35}$诱导的大鼠神经元炎性反应,使炎性因子IL-1β和TNF-α表达水平下降,同时可通过抑制核转录因子κB(nuclear transcription factor κB,NF-κB)活化水平减轻神经炎性反应[20]。有研究表明[21],长时间Asp治疗可使AD大鼠受损记忆得到一定恢复,同时改善突触功能障碍。Asp诱生型脂氧素A4对AD小鼠作用的研究显示,NF-κB活化、促炎因子和趋化因子表达均减少,而IL-10表达水平增加[22]。我们的研究结果也显示,通过Asp干预可使大鼠水迷宫实验逃避潜伏期较模型组缩短,且差异有统计学意义,提示Asp干预对Aβ诱导的AD模型大鼠空间学习记忆能力可能具有一定的保护和改善功能。尽管多项研究认为没有充足证据支持Asp对AD有防治作用[23,24],但Wang等[25]则肯定了Asp对AD的积极影响,尤其是长期使用Asp可显著减低人群AD的发生率。本研究结果表明Asp对AD干预的起始时间、持续时间以及药物剂量是影响是否获益及获益程度的因素。

本研究提示,促炎/抗炎因子之间的微妙平衡可能决定了炎性反应在AD进程中的角色,Asp干预使AD大鼠空间学习记忆能力得以改善,同时可能通过抑制神经胶质细胞活化水平和炎性反应,使IL-4和IL-10表达水平提高。Asp在AD防治中的作用尚存争议,更为科学的临床试验设计仍是今后研究中不可忽视的内容。

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