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孕晚期暴露脂多糖对后代衰老相关认知改变的跨代遗传效应

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摘要 **目的** 探讨小鼠孕晚期暴露脂多糖对后代年龄相关认知改变的影响,并探究是否存在性别特异性的遗传效应。**方法** 对孕第 15 ~ 17 天的美国肿瘤研究协会小鼠(ICR)CD-1 母鼠(F0)每天注射脂多糖(LPS 组,50 μg/kg),或等容积生理盐水(CON 组)。分娩的子鼠(F1)2 月龄时,随机抽取 LPS 处理小鼠(F1-LPS,雌雄)与年龄匹配的野生型 CD-1 小鼠杂交,非同窝的 F1-LPS 雄性和雌性杂交、F1-CON 雄性和雌性杂交,得到不同系别 F2 代。同样,F2-LPS 小鼠继续与野生型小鼠交配孕育 F3 代。上述小鼠常规饲养至 3 月龄和 18 月龄时,随机抽取 F1、F2 和 F3 代小鼠(每组 $n=8$)完成 Morris 迷宫实验,检测小鼠学习和记忆能力。**结果** 与 3 月龄 CON 小鼠相比,18 月龄 CON 小鼠的学习和记忆能力较差(尤其是雌鼠)。F1 代小鼠中,3 月龄和 18 月龄 F1-LPS 小鼠的学习和记忆力差于同龄 CON 小鼠。F2 代小鼠中,3 月龄 F2-LPS 双系小鼠学习和记忆力差于同龄 CON 小鼠,F2-LPS 父系小鼠仅记忆力差于同龄 CON 组。18 月龄 F2-LPS 父系和 F2-LPS 双系小鼠学习和记忆力差于同龄 CON 小鼠,F2-LPS 母系雄鼠学习和记忆力差于 CON 雄鼠,F2-LPS 母系小鼠记忆力强于 F2-LPS 双系小鼠。F3 代小鼠中,3 月龄 F3-LPS 双系小鼠记忆力差于同龄 CON 小鼠。18 月龄 F3-LPS 父系和 F3-LPS 双系小鼠学习和记忆力差于同龄 CON 小鼠。18 月龄 F3-LPS 母系和父系雄鼠记忆力好于 F3-LPS 双系雄鼠。**结论** 孕晚期脂多糖暴露会加速后代小鼠衰老相关认知改变,这种现象具有跨代遗传效应,且存在性别差异,主要体现在父系遗传中。

关键词 衰老;学习;记忆;脂多糖;跨代遗传效应;小鼠

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随着人类社会老龄化加剧,衰老相关认知减退(age-association cognition decline, AACD)严重影响老年人的生活质量,也是老年性痴呆的危险因素。目前认为这种改变具有异质性,可能涉及遗传和环境双重作用机制[1]。大量研究[2-3]表明,生命早期不良因素暴露(如感染、心理应激等)会影响神经系统发育进程,增加成年后神经精神系统疾病的易感性,加速个体认知损害甚至阿尔茨海默病的发生[4]。这些改变可能存在多代传递现象,甚至未直接接触不良因素的后代也会出现疾病表型(跨代遗传效应)[5]。该课题组前期研究[6-7]表明,孕晚期 CD-1 母鼠(F0)暴露脂多糖(LPS)加剧其子代(F1)和孙代(F2)小鼠老年期认知功能减退。F0(孕期母体)、F1(发育胚胎)和 F2(生殖细胞)代属于多代暴露,F3 代未直接接触不良因素,属于跨代继承的一代。孕晚期 LPS 暴露对后代 AACD 的影响是否存在跨代遗传效应及性别差异,目前暂未见相关文献报告。因此,该研究利用孕晚期 CD-1 小鼠采用脂多糖诱导的妊娠期炎症模型,探究其 F1、F2 和 F3 代小鼠年龄相关认知功能,以其验证是否存在跨代遗传效应及性别差异。

1 材料与方法

1.1 实验动物 2 月龄 CD-1 小鼠购自北京维通利华实验动物有限公司,体质量为 22 ~ 26 g,饲养温度为(25 ± 2)℃,湿度(55 ± 10)%,12 h 光照/12 h 黑暗周期,小鼠自由进食和饮水。该实验操作符合安徽医科大学动物实验伦理委员会要求(批号:LLSC20160165)。

1.2 实验设计与分组 小鼠适应性喂养 2 周后,按雌雄比 2∶1 合笼交配,首次检查阴栓定为受孕第 0 天(GD 0)。将孕鼠(F0)分为 2 组:细菌脂多糖(LPS)组和生理盐水(CON)组(每组 20 只),小鼠孕晚期(GD 15 ~ 17)每天一次腹腔注射等剂量的 LPS

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或生理盐水(50 μg/kg)。分娩的子鼠(F1)2 月龄时,随机抽取 LPS 处理小鼠(F1-LPS,雌雄)与年龄匹配的野生型 CD-1 小鼠杂交,非同窝的 F1-LPS 雄性和雌性杂交、F1-CON 雄性和雌性杂交,得到不同系别 F2 代,即母系 F2(F2-LPS 母系,F1-LPS 雌性与正常雄性交配)、双系 F2 (F2-LPS 双系,F1-LPS 雄性与非同窝 F1-LPS 雌性交配)、父系 F2(F2-LPS 父系,F1-LPS 雄性与正常雌性)和对照 F2(F2-CON,F1-CON 雌性与雄性交配)。F2-LPS 小鼠继续与野生型小鼠交配孕育 F3 代,命名如下:母系 F3(F3-LPS 母系,F2-LPS 母系雌性与正常雄性交配)、双系 F3(F3-LPS 双系,F2-LPS 双系雄性与非同窝 F2-LPS 双系雌性交配)、父系 F3(F3-LPS 父系,F2-LPS 父系雄性与正常雌性小鼠交配)和对照 F3(F3-CON,F1-CON 雌性与雄性交配)。F2 和 F3 代小鼠均在出生后第 21 天与母亲分笼,同性别每笼 3 ~ 4 只常规饲养。上述小鼠饲养至 3 月龄和 18 月龄时,随机选取 F1、F2 和 F3 代(每组 $n = 8$)完成 Morris 迷宫实验。实验流程示意图如图 1。

1.3 Morris 水迷宫(MWM)实验 MWM 是评价小鼠空间学习记忆能力最常用的软件。水迷宫装置由一个圆形水槽(直径 120 cm,高 30 cm)、圆柱形逃生平台(直径 10 cm,高 24 cm)组成。水槽的四周用白色窗帘围起,3 个黑色的明显的线索(圆形、正方形和三角形)贴在窗帘上,摄像头安装在水箱上方。MWM 实验主要包括定位航行实验和空间探索实验两部分,分别对小鼠进行空间学习和记忆能力的检测。

1.3.1 *定位航行实验* 将水槽中充满水,控制水温在 22 ℃左右。迷宫被分为四个象限(Ⅰ、Ⅱ、Ⅲ、Ⅳ象限),将平台固定在第Ⅰ象限内,使平台位于水下 1 cm。将小鼠面朝桶壁放入水中,游泳 60 s,每天进行 4 次实验,每次入水象限均不相同,每次间隔 15 min,持续 7 d。每次开始测试后,无论小鼠在 60 s 内能否找到平台,都让小鼠在平台上休息 30 s。使用 ANY-maze 软件记录小鼠的游泳潜伏期和游泳路程。

1.3.2 *空间探索实验* 小鼠完成第 7 天定位航行任务以后,休息 1 h,取出平台,将小鼠从平台所在象限的相反象限(第Ⅲ象限)放入水中。使其自由探索 60 s,记录小鼠在第Ⅰ象限(靶象限)内的游泳路程和游泳时间,计算出相应的游泳路程百分比和游泳时间百分比。

1.4 统计学处理 所有数据统计分析采用 SPSS 21 完成。对所有数据进行正态性检验(Kolmogorov-Smirnov test),符合正态性分布用 $\bar{x} \pm s$ 表示。使用

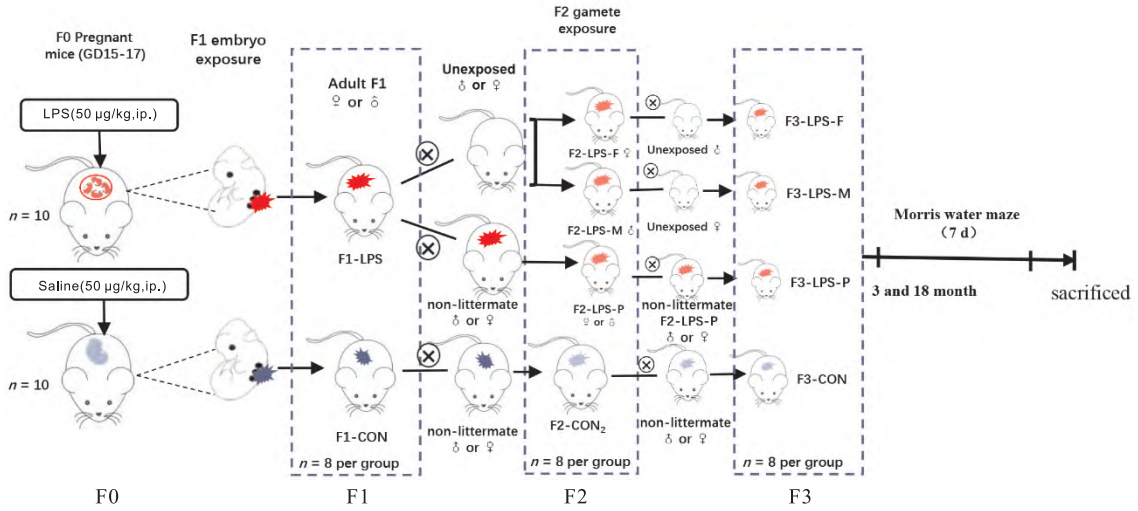

图 1 小鼠实验的流程图

Fig. 1 The timeline of experimental events

CON-F: The female mice were exposed to saline in F1 generation; CON-M: The male mice were exposed to saline in F1 generation; LPS-F: The female mice were exposed to LPS in F1 generation; LPS-M: The male mice were exposed to LPS in F1 generation; F2-CON: The mice for whose parents were exposed to saline in utero; F2-LPS-F: The mice for whose mother was exposed to inflammation in utero; F2-LPS-M: The mice for whose father was exposed to inflammation in utero; F2-LPS-P: The mice for whose parents was exposed to inflammation in utero; F3-CON: The mice for whose parents is F2-CON; F3-LPS-F: The mice for whose mother is F2-LPS-F; F3-LPS-M: The mice for whose father is F2-LPS-M; F3-LPS-P: The mice for whose parents are non-littermate F2-LPS-P; MWM:Morris water maze; LPS:lipopolysaccharide; ip:intraperitoneal; GD:gestational day.

重复测定方差分析(rm-ANOVA)、单因素或双因素方差(One/Two way ANOVA)分析,组间两两比较采用 LSD-*t* 检验。$P<0.05$ 为差异有统计学意义。

2 结果

2.1 年龄效应 在 F1、F2 和 F3 代小鼠中,学习期游泳潜伏期和游泳路程随着时间的增加逐渐降低($P<0.01$),表明所有小鼠具有学习水迷宫的能力。在 F1 代小鼠中 18 月龄 CON-F 和 CON-M 组小鼠学习期的游泳潜伏期和游泳路程显著长于 3 月龄 CON-F[$F_{(1,14)}=27.634$, $P<0.01$; $F_{(1,14)}=11.771$, $P=0.004$]和 CON-M 组小鼠[$F_{(1,14)}=6.251$, $P=0.025$; $F_{(1,14)}=12.513$, $P=0.003$],见图 2A－2D。小鼠记忆期靶象限游泳路程百分比[$F_{(1,28)}=76.15$, $P<0.001$]和游泳时间百分比[$F_{(1,28)}=65.99$, $P<0.001$]有显著的年龄差异,即老年(18 月龄)小鼠的靶象限内游泳时间百分比和路程百分比显著低于 3 月龄小鼠($P_s<0.05$),见图 2E－2F。而且,18 月龄 CON 组雄性小鼠靶象限内游泳时间百分比和游泳路程百分比高于同龄雌性小鼠($P<0.05$)。

2.2 处理效应

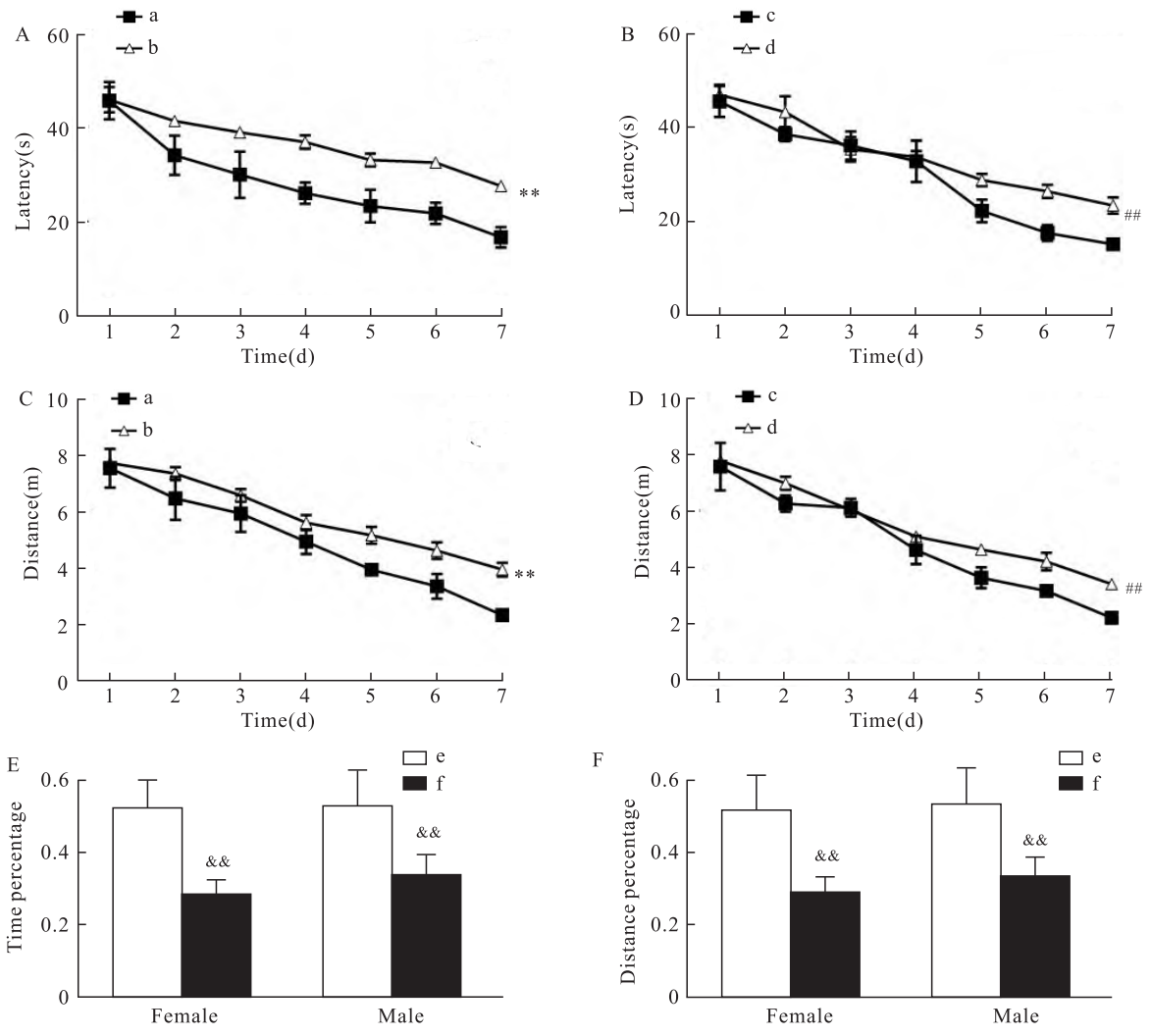

图 2 CD-1 小鼠在水迷宫学习记忆能力测试中的年龄效应

Fig. 2 Age-related impact on the learning and memory abilities of CD-1 mice in MWM test

A, C: The age effects of swimming latency and swimming distance in the learning period of female mice; B, D: The age effects of swimming latency and swimming distance in the learning period of male mice; E, F: The percentage of swimming distance and time in the target quadrant of the memory period of the control group during aging; a: 3CON-F group; b: 18CON-F group; c: 3CON-M group; d: 18CON-M group; e: 3CON group; f: 18CON group; $^{**}P<0.01$ *vs* 3CON-F group; $^{\#\#}P<0.01$ *vs* 3CON-M group; $^{\&\&}P<0.01$ *vs* 3CON group.

2.2.1 F1 代小鼠处理组间效应 对于 F1 代小鼠，3 月龄 LPS-M 小鼠在学习期仅游泳路程长于 3 月龄 CON-M 小鼠（$P=0.043$）。3 月龄 LPS-M 和 LPS-F 小鼠记忆期的靶象限内游泳时间和游泳路程百分比与 CON 组相比差异有统计学意义，表现为 LPS-M 和 LPS-F 的时间百分比（$P=0.001$，$P<0.01$）和路程百分比（$P=0.003$，$P<0.01$）显著低于同性别 CON 组小鼠（图 3A－3D）。18 月龄 F1-LPS 与 F1-CON 小鼠学习期的游泳潜伏期和游泳路程差异有统计学意义（$P<0.01$），表现为 18 月龄 LPS-M 和 LPS-F 小鼠的游泳潜伏期和路程长于 CON-M（$P<0.01$）和 CON-F 组（$P<0.05$）小鼠。18 月龄 F1-LPS 小鼠与 F1-CON 组小鼠的记忆期表现也存在差异有统计学意义［$F_{(3,28)}=11.527$、8.497，$P_s<0.01$］，表现为 LPS 组雌雄小鼠靶象限内游泳时间和路程百分比分别显著低于同性别 CON 组小鼠（$P<0.01$），见图 3E－3H。

2.2.2 F2代小鼠处理组间效应 对于F2代小鼠，

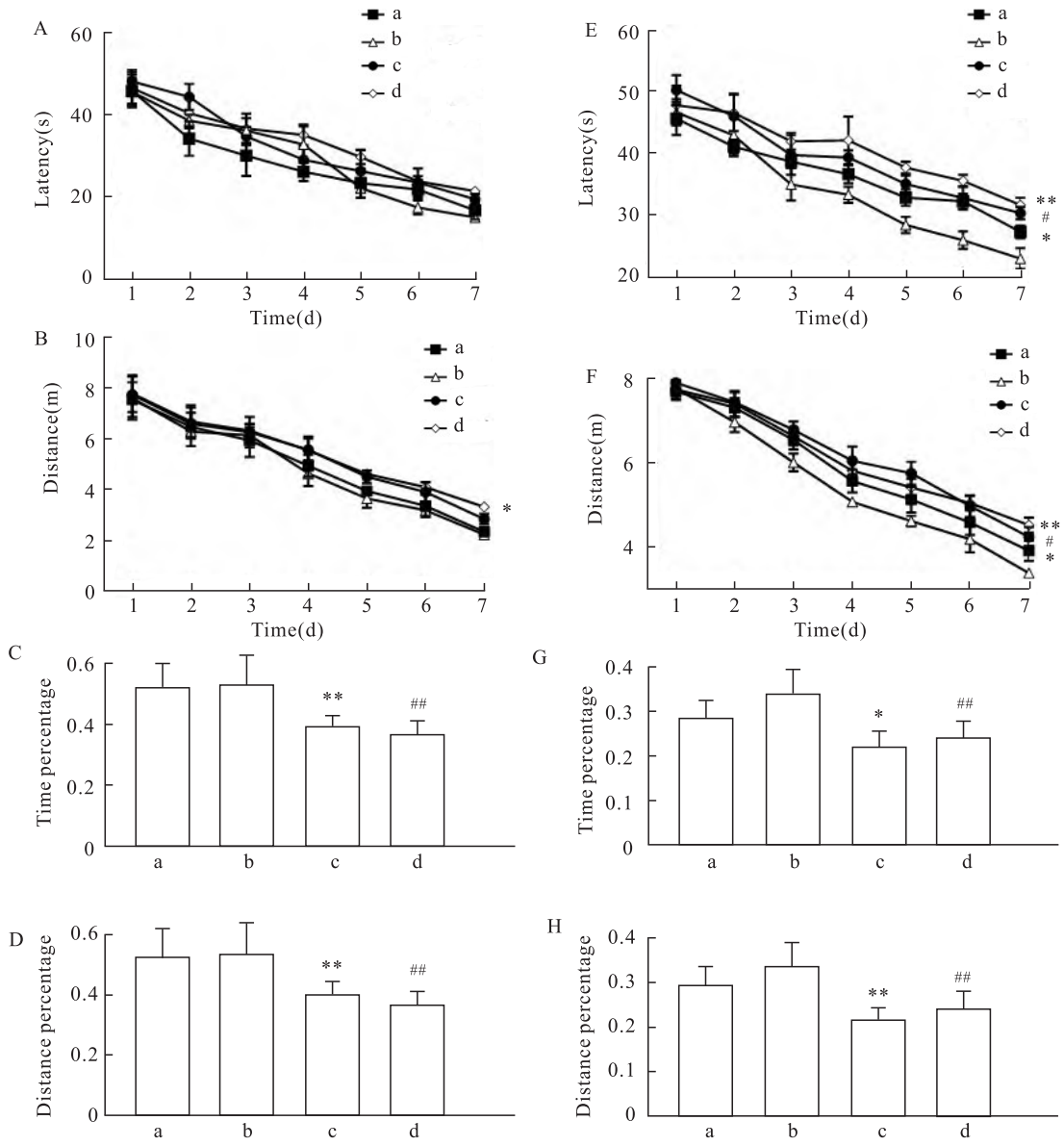

图 3 F1 代小鼠在 MWM 中的学习和记忆表现

Fig. 3 Learning and memory performance of the F1 generation in the MWM test

A－D: Learning phase (Escape latency and distance swam) and memory phase (percentage swimming time and distance swam in the target quadrant) at 3 months; E－H: 18 months of the MWM test in the F1 generation; a: CON-F group; b: CON-M group; c: LPS-F group; d: LPS-M group; $^{*}P<0.05$, $^{**}P<0.01$ *vs* CON-F group; $^{\#}P<0.05$, $^{\#\#}P<0.01$ *vs* CON-M group.

3 月龄小鼠中,F2-CON 组雌雄小鼠的游泳潜伏期(P =0.014、0.012)和游泳路程(P =0.002、0.006)均显著短于 F2-LPS-双系雌雄小鼠(图 4A－4D)。3 月龄 F2-CON 组雌雄小鼠靶象限游泳路程百分比(P =0.002、0.001; P =0.006、0.001)和时间百分比(P =0.005、0.004; P =0.026、0.005)显著长于 F2-LPS 父系和 F2-LPS 双系雌雄小鼠(图 4E－4F)。

18 月龄 F2 代小鼠中,在学习期,F2-CON 组雄鼠游泳潜伏期和游泳路程短于 F2-LPS 母系(P =0.042、0.036)、F2-LPS 父系(P =0.024、0.016)和 F2-LPS 双系雄性小鼠(P =0.003、0.006)。F2-CON 组雌鼠游泳潜伏期和游泳路程短于 F2-LPS 父系(P <0.05)和 F2-LPS 双系雄性小鼠(P <0.01)。此外,在游泳路程上,F2-CON 组雌性小鼠的游泳路程也短于 F2-LPS 母系雌性小鼠(P =0.032),见图 5A-5D。在记忆期,18 月龄各组小鼠之间的靶象限内游泳时间百分比[$F_{(3,28)}$ =4.654、3.958; P =0.009、0.018]和路程百分比[$F_{(3,28)}$ =7.426、4.894; P =0.001、0.007]差异有统计学意义。F2-CON 组雌雄小鼠的时间百分比和路程百分比显著高于 F2-LPS-父系(P =0.008、0.001; P =0.013、0.006)和 F2-LPS-双系(P =0.002、0.001; P =0.004、0.002)。

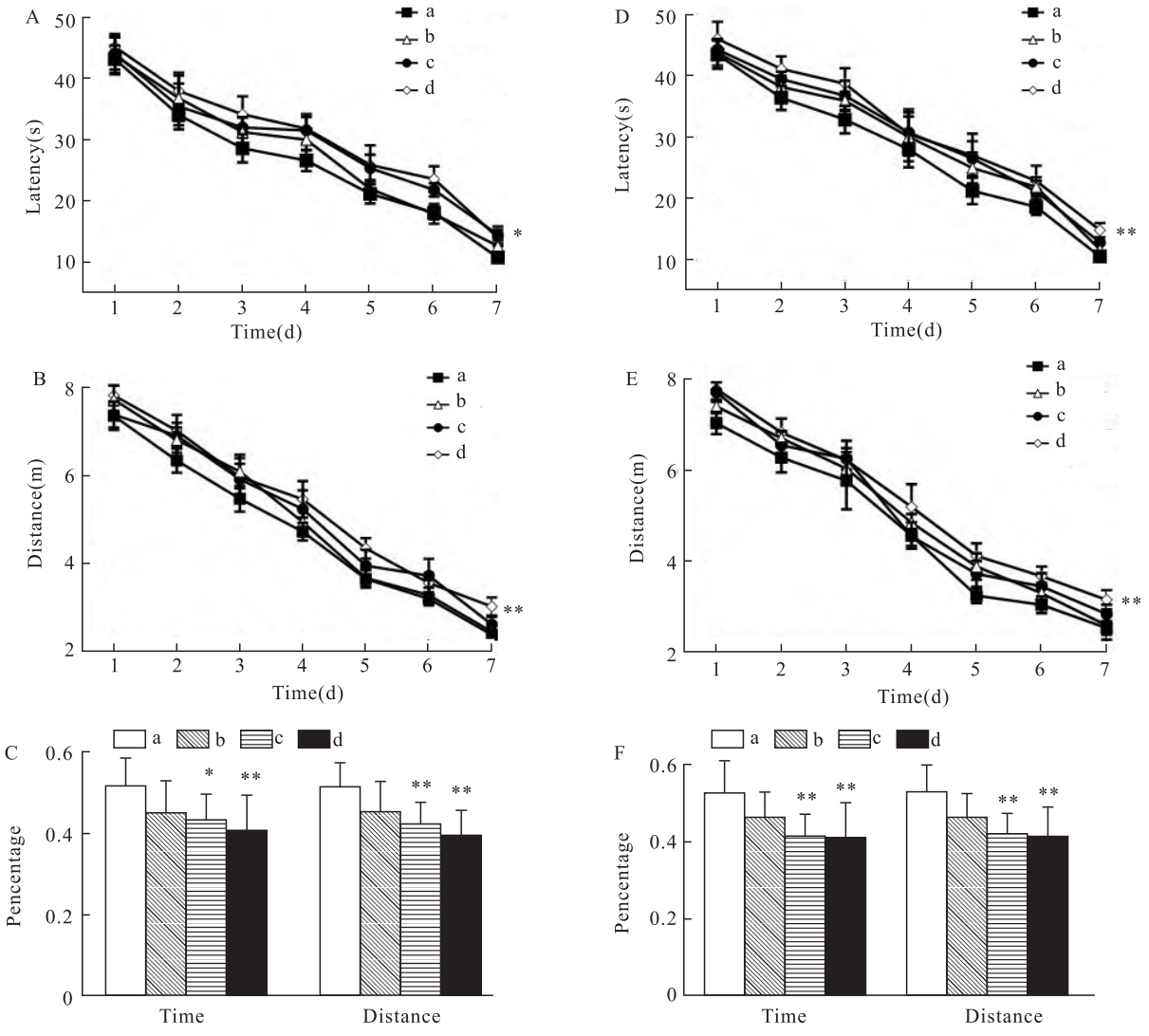

图 4　F2 代 3 月龄小鼠学习记忆能力的组间效应

Fig. 4　Intergroup effect on learning and memory ability of 3-month-old mice in F2 generation

A－C: The swimming latency and swimming distance of 3-month-old female mice during the learning phase (A, B), and the percentage of swimming distance and time in the target quadrant during the memory phase (C); D－F: The performance of learning (D, E) and memory phase (F) in 3-month-old male mice; a: F2-CON group; b: F2-LPS-F group; c: F2-LPS-M group; d: F2-LPS-P group; $^{*}P$ <0.05, $^{**}P$ <0.01 *vs* F2-CON group.

F2-LPS 母系雄鼠的游泳路程百分比低于 F2-CON 组雄鼠(P = 0.047)而高于 F2-LPS 双系雄鼠(P = 0.031)。F2-LPS 母系组雌鼠的游泳路程百分比也高于 F2-LPS 双系组雌鼠(P = 0.049),见图 5E – 5F。

2.2.3 F3 代小鼠处理组间效应 对于 F3 代小鼠,在 3 月龄时,仅 F3-CON 雌雄小鼠记忆期游泳时间百分比和路程百分比显著高于 F3-LPS 双系小鼠(P =0.005、0.002; P =0.006、0.002)。见图 6。

在 18 月龄时,F3-CON 组雌雄小鼠的游泳潜伏期和游泳路程均显著短于 F3-LPS-父系和 F3-LPS-双系小鼠的游泳潜伏期(P = 0.013、0.007; P = 0.014、0.002)和游泳路程(P = 0.015、0.001; P = 0.027、0.002),见图 7A – 7D。与 F3-LPS 双系小鼠相比,18 月龄 F3-CON 雌雄小鼠具有较高的游泳时间百分比(P =0.001、0.025)和游泳路程百分比(P =0.001、0.005)。F3-CON 雌雄小鼠的游泳路程百分比也高于 F3-LPS 父系小鼠(P = 0.032、0.031)。F3-LPS 母系雄性小鼠的游泳时间百分比和路程百分比高于 F3-LPS 双系雄性小鼠(P =0.027、0.004),

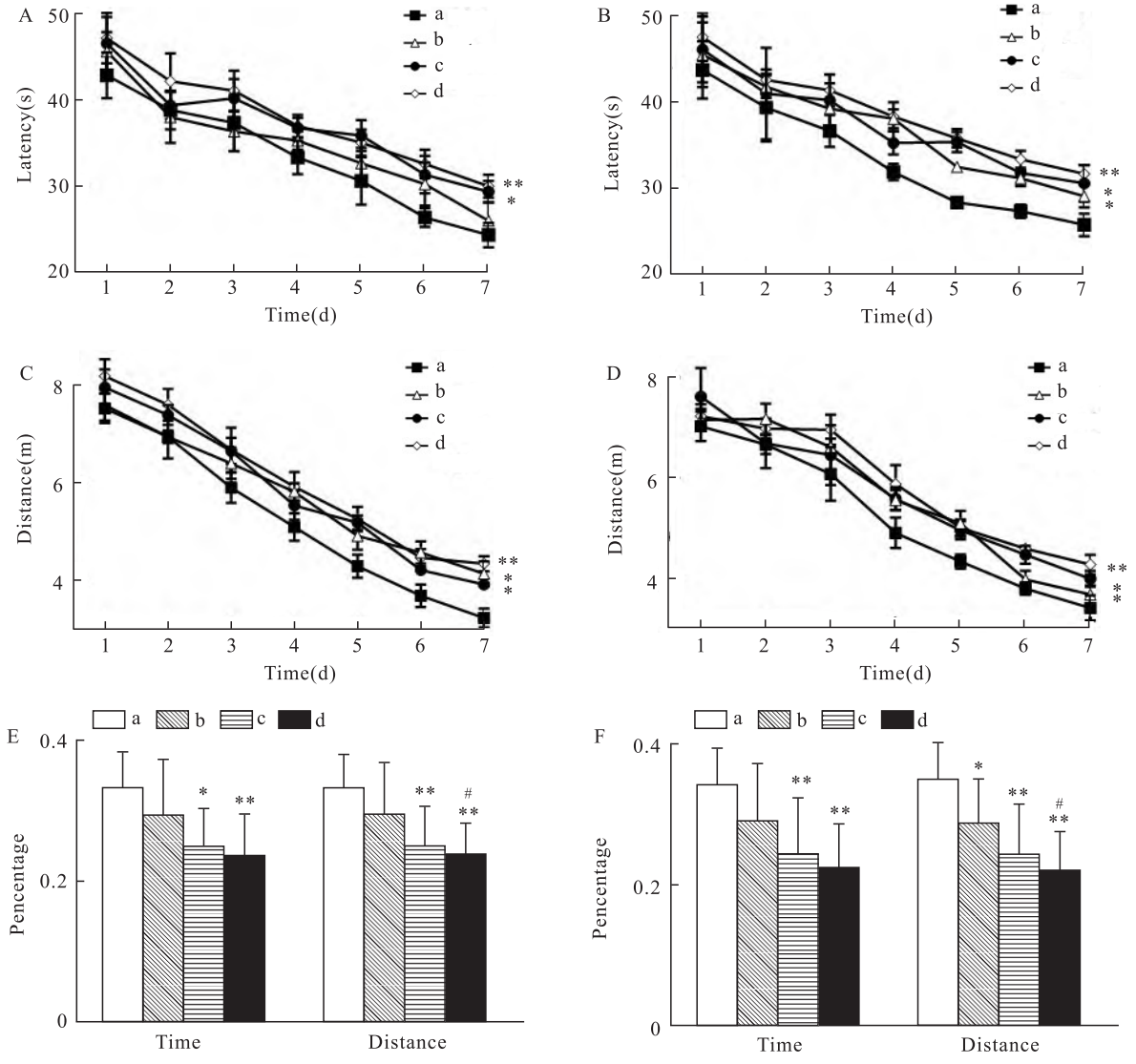

图 5 F2 代 18 月龄小鼠学习记忆能力的组间效应

Fig. 5 Intergroup effect on learning and memory ability of 18-month-old mice in F2 generation

A – C:The swimming latency and swimming distance of 18-month-old female mice during the learning phase (A, B), and the percentage of swimming distance and time in the target quadrant during the memory phase (C); D – F:The performance of learning (D, E) and memory phase (F) in 18-month-old male mice; a: F2-CON group; b: F2-LPS-F group; c: F2-LPS-M group; d: F2-LPS-P group; $^{*}P<0.05$, $^{**}P<0.01$ *vs* F2-CON group; $^{\#}P<0.05$ *vs* F2-LPS-F group.

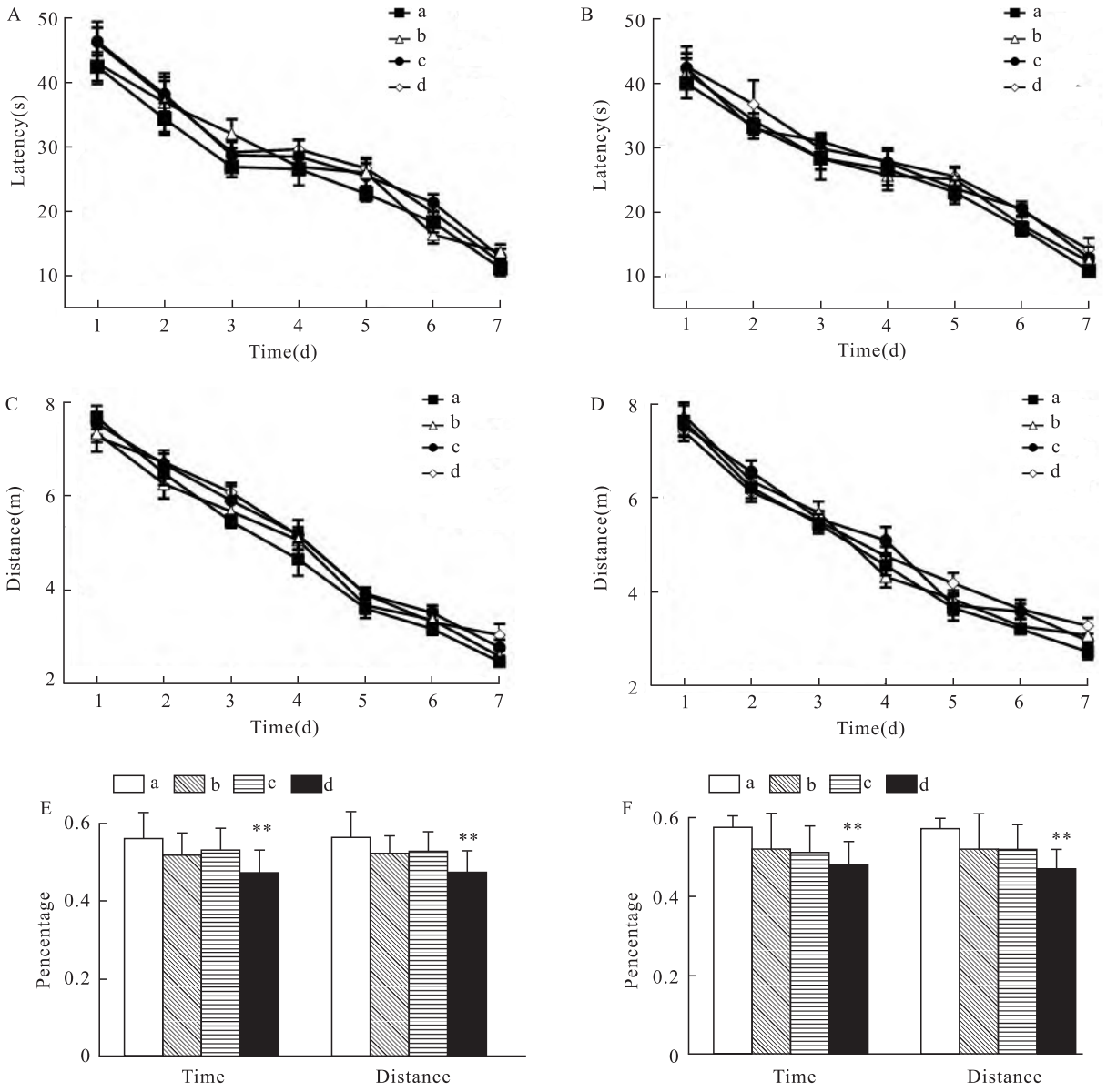

图 6　F3 代 3 月龄小鼠学习记忆能力的组间效应

Fig. 6　Intergroup effect on learning and memory ability of 3-month-old mice in F3 generation

A – C: The swimming latency and swimming distance of 3-month-old female mice during the learning phase (A, B), and the percentage of swimming distance and time in the target quadrant during the memory phase (C); D – F: The performance of learning (D, E) and memory phase (F) in 3-month-old male mice; a: F3-CON group; b: F3-LPS-F group; c: F3-LPS-M group; d: F3-LPS-P group; $^{**}P<0.01$ *vs* F3-CON group.

见图 7A – 7D。F3-LPS 父系雄性小鼠的游泳路程百分比也显著高于 F3-LPS 双系雄性小鼠(P = 0.035),见图 7E – 7F。

3　讨论

人类和啮齿类动物正常衰老过程中往往伴随着一系列认知功能的改变,尤其是学习和记忆能力减退[8],这些改变也常见于一些中枢神经系统退行性疾病(如阿尔茨海默病、额颞叶痴呆)。大量研究[9-10]表明,孕期不良因素暴露可使子代宫内表观遗传编程改变,导致成年某些疾病易感性增加,且这种现象可能存在跨代遗传效应,表观遗传修饰改变(尤其是 DNA 甲基化、组蛋白修饰、非编码 RNA)发挥重要作用[11]。比如,C57BL/6J 雄鼠腹膜内注射聚胞苷酸(模拟病毒免疫攻击),会对子代和孙代小鼠的大脑和行为产生影响,可能由精子小非编码

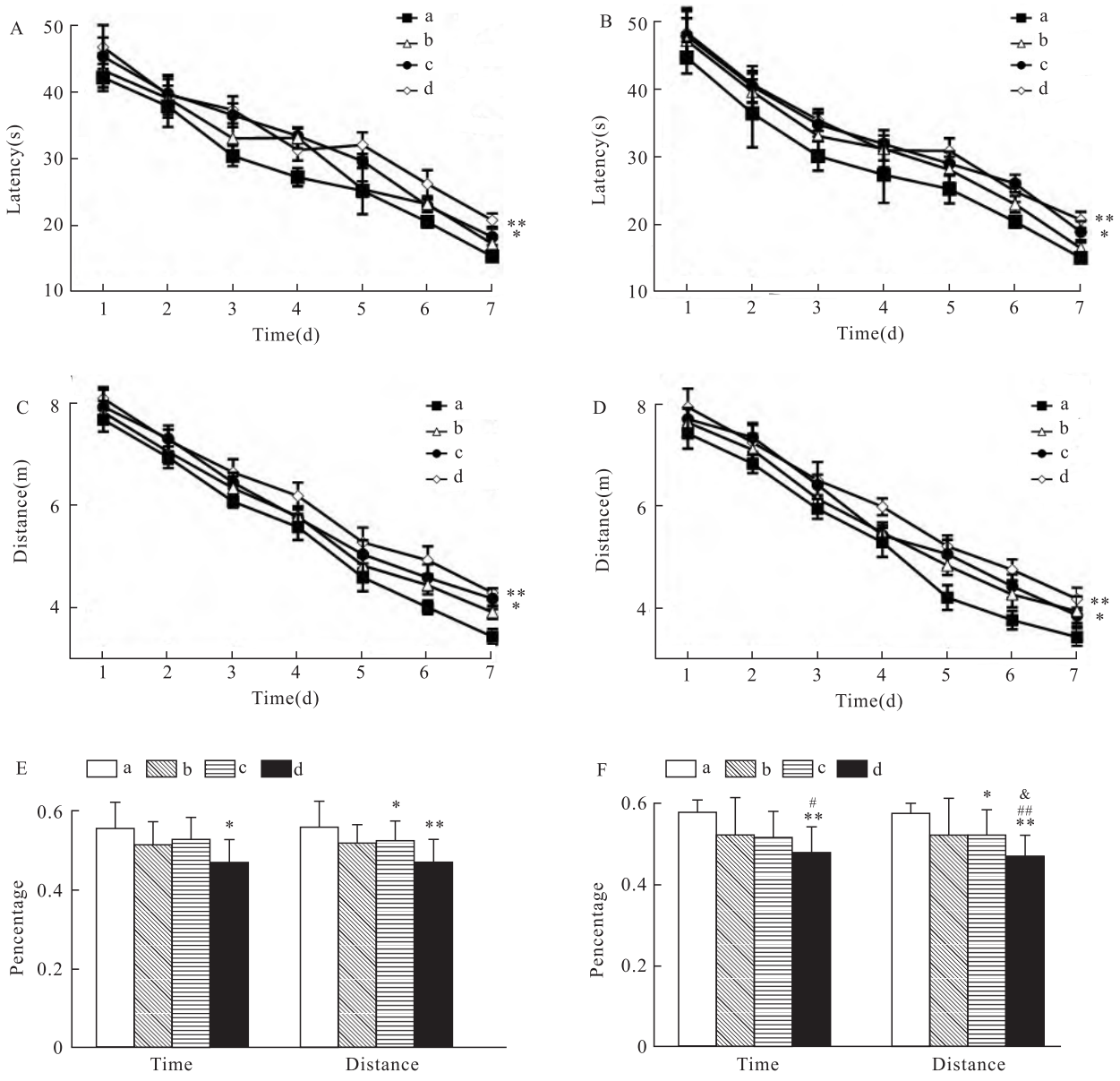

图 7　F3 代 18 月龄小鼠学习记忆能力的组间效应

Fig. 7　Intergroup effect on learning and memory ability of 18-month-old mice in F3 generation

A – C: The swimming latency and swimming distance of 3-month-old female mice during the learning phase (A, B), and the percentage of swimming distance and time in the target quadrant during the memory phase (C); D – F: The performance of learning (D, E) and memory phase (F) in 3-month-old male mice; a: F3-CON group; b: F3-LPS-F group; c: F3-LPS-M group; d: F3-LPS-P group; $^{*}P<0.05$, $^{**}P<0.01$ *vs* F3-CON group; $^{\#}P<0.05$, $^{\#\#}P<0.01$ *vs* F3-LPS-F group; $^{\&}P<0.05$ *vs* F3-LPS-M group.

RNA 含量的变化介导的[12]。该课题组研究也表明,孕晚期 CD-1 小鼠(F0)暴露 LPS(腹腔内注射,诱导炎症模型),可以加速子代(F1)和孙代(F2)小鼠 AACD,甚至 AD 样病理生理改变,可能涉及脑内突触相关蛋白改变和表观遗传修饰机制[13-15]。既往研究[7]表明小鼠孕晚期 LPS 暴露通过表观遗传修饰机制加速子代及其孙代的年龄相关性认知功能减退,该研究进一步拓展,利用孕晚期暴露 LPS 的小鼠模型对后代认知障碍风险进行了谱系差异的初步评估,明确是否存在跨代遗传效应及性别效应。

该研究中,与青年小鼠相比,老年小鼠的学习和记忆能力明显下降,表明小鼠的学习记忆能力随着年龄增长而减退。胚胎期暴露 LPS 的子鼠(F1 代)学习记忆能力比同龄对照组更差,说明孕期 LPS 处理加速子鼠的认知减退,与既往相关文献[6-7]报道一致。重要的是,正常衰老小鼠的学习记忆能力有

显著的性别差异,表现为雌鼠认知下降更为明显,但孕期 LPS 处理小鼠的后代(F1、F2 和 F3)老年期学习记忆能力改变不存在性别差异,提示 LPS 处理可能对雄鼠认知损害影响更大。孕期 LPS 暴露对后代成年认知障碍影响的严重程度取决于受 LPS 影响的谱系(F1 男性或女性)。具体表现在:F2 代也是直接受到 LPS 处理影响的一代,在青年期双系和父系小鼠的学习和记忆能力较对照组更差,而母系小鼠与对照组之间未见显著差异。到了老年期,母系小鼠、父系和双系小鼠的学习记忆能力均差于对照组小鼠。F3 代作为跨带遗传的第一代小鼠,间接受到 LPS 的影响,青年期仅 LPS 双系小鼠记忆力差于同龄对照组小鼠,但到了老年期,父系和双系小鼠的学习和记忆能力显著差于对照组小鼠,在记忆力上,母系和父系雄鼠的记忆力好于双系小鼠。因此,该研究推测母鼠妊娠晚期 LPS 处理可加重其后代小鼠的年龄相关性学习记忆能力,并能跨代影响到 F3 代小鼠的认知行为,尤其是雄性小鼠的后代。而且,这种行为学表型有一定的累加效应,即双系小鼠的后代年龄相关性学习记忆能力恶化比父系或母系小鼠更严重。上述改变的机制暂不明确,跨代表观遗传改变是否参与其中也有待进一步研究。

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Transgenerational genetic effects of exposure to lipopolysaccharides in late pregnancy on age-related cognitive changes in offspring

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Abstract ***Objective*** To explore the effects of exposure to lipopolysaccharides in late pregnancy on age-related cognitive changes in offspring of mice, and to investigate whether there is a gender specific genetic effect. ***Methods*** Institute of cancer research(ICR)CD-1 mice during gestational days 15 – 17 were injected with lipopolysaccharide daily (LPS group, 50 μg/kg), or equal volume of normal saline (CON group). At the age of 2 months after their delivery, LPS treated offspring mice (F1-LPS, male and female) were randomly selected and hybridized with age-matched wild-type CD-1 mice. F1-LPS males and females with different littermates, and F1-CON males and females were hybridized to obtain F2 generations of different lineages. Similarly, F2-LPS mice were mated with wild-type mice to conceive the F3 generation. At the age of 3 and 18 months old, F1, F2, and F3 mice ($n=8$ in each group) were randomly selected to complete the Morris maze experiment in order to test their cognitive abilities. ***Results*** Compared with 3-month-old CON mice, 18-month-old CON mice showed poorer learning and memory abilities, especially in females. For F1 generation, the learning and memory abilities of the 3-month-old and 18-month-old F1-LPS mice were inferior to those of the same aged CON mice. For F2 generation, the 3-month-old F2-LPS-parental mice had poorer learning and memory compared to the same aged CON mice, while the F2-LPS-paternal mice only had poorer memory compared to the same aged CON group. The learning and memory abilities of 18-month-old F2-LPS paternal and F2-LPS-parental mice were inferior to those of the same aged CON mice. The learning and memory abilities of F2-LPS maternal male mice were inferior to those of CON male mice, and the memory abilities of F2-LPS maternal mice were stronger than those of F2-LPS-parental mice. With regards to the F3 generation, the memory of the 3-month-old F3-LPS-parental mice was poorer than that of the same aged CON mice. The learning and memory abilities of F3-LPS paternal and F3-LPS-parental mice at 18 months old were inferior to those of CON mice of the same age. The 18-month-old F3-LPS maternal and paternal male mice had better memory than F3-LPS-parental male mice. ***Conclusion*** Exposure to lipopolysaccharides in late pregnancy can accelerate age-related cognitive decline in offspring mice, and it has a cross generational genetic effect and gender differences, mainly in paternal inheritance.

Key words aging; learning; memory; lipopolysaccharides; transgenerational genetic effects; mice

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