

·基础研究·

紫云英苷抑制APP/PS1小鼠大脑皮质神经元凋亡

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摘要:【目的】探讨紫云英苷(AST)对APP/PS1转基因小鼠大脑皮质神经元凋亡的影响。【方法】将18只6月龄雄性APP/PS1转基因小鼠随机分为APP/PS1、APP/PS1+40 mg/kg AST、APP/PS1+20 mg/kg DNP(Donepezil, DNP)三组,每组各6只动物。同时另选6只同月龄C57BL/6雄性小鼠作为正常对照组(Control)。腹腔注射给药AST,每日一次,连续给药一个月后,Tunel染色法检测APP/PS1小鼠大脑皮质内神经元凋亡情况;免疫荧光染色法检测APP/PS1小鼠大脑皮质内神经元凋亡相关蛋白*Bax*、*Bcl-2*、*Caspase9*、*Cleaved-Caspase3*表达情况;Western blot法检测APP/PS1小鼠大脑皮质内*Bax*、*Bcl-2*、*Caspase9*及*Caspase3*表达水平的变化。【结果】Tunel染色结果显示,40 mg/kg AST及20 mg/kg DNP均可减少APP/PS1小鼠大脑皮质内神经元凋亡,其中AST抑制效果尤为明显。免疫荧光染色结果表明,40 mg/kg AST及20 mg/kg DNP均抑制APP/PS1小鼠大脑皮质内神经元中*Bax*、*Caspase9*及*Cleaved-Caspase3*的表达,增加*Bcl-2*的表达。Western blot结果进一步证实,40 mg/kg AST及20 mg/kg DNP均可下调APP/PS1小鼠大脑皮质内神经元*Bax* ($P < 0.05$, $P < 0.05$)、*Caspase9* ($P < 0.005$, $P < 0.05$)及*Caspase3* ($P < 0.0001$, $P < 0.0001$),上调*Bcl-2* ($P < 0.05$, $P < 0.05$)。【结论】AST能够抑制APP/PS1小鼠大脑皮质神经元凋亡。

关键词:紫云英苷;APP/PS1小鼠;大脑皮质;神经元;凋亡

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Astragalín Inhibits Apoptosis of Cerebral Cortex Neurons in APP/PS1 Mice

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Abstract:【Objective】To investigate the effect of Astragalín (AST) on apoptosis of cerebral cortex neurons in APP/PS1 transgenic mice.【Methods】Eighteen six-month-old male APP/PS1 transgenic mice were randomly divided into APP/PS1 group, APP/PS1+40 mg/kg AST group and APP/PS1+20 mg/kg Donepezil (DNP) group, with six mice in each group. At the same time, six male C57BL/6 mice were selected as the normal control group. After intraperitoneal injection of AST once a day and continuous administration for one month, we used Tunel staining to detect the apoptosis of neurons in the cerebral cortex of APP/PS1 mice; immunofluorescent staining to examine the expression of apoptosis-related proteins *Bax*, *Bcl-2*, *Caspase9* and *Cleaved-Caspase3* in the cerebral cortex neurons of APP/PS1 mice; Western blot method to evaluate the changes of the expression of *Bax*, *Bcl-2*, *Caspase9* and *Caspase3*.【Results】Tunel staining showed that 40 mg/kg AST and 20 mg/kg DNP both reduced the apoptosis of neurons in the cerebral cortex of APP/PS1 mice, AST with more significant inhibition effect. Immunofluorescent staining revealed that 40 mg/kg AST and 20 mg/kg DNP both inhibit-

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ed the expression of *Bax*, *Caspase9*, and *Cleaved-Caspase3*, and increased the expression of *Bcl-2* in the cerebral cortex neurons of APP/PS1 mice. Western blot results further confirmed that 40 mg/kg AST and 20 mg/kg DNP both down-regulated the expression of *Bax* ($P < 0.05$, $P < 0.05$), *Caspase9* ($P < 0.005$, $P < 0.05$) and *Caspase3* ($P < 0.0001$, $P < 0.0001$), and up-regulated the expression of *Bcl-2* ($P < 0.05$, $P < 0.05$) in the cerebral cortex neurons of APP/PS1 mice. [Conclusions] AST can inhibit the apoptosis of cerebral cortex neurons in APP/PS1 mice.

Key words: astragalín (AST); APP/PS1 mice; cerebral cortex; neuron; apoptosis

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阿尔茨海默病 (Alzheimer's disease, AD) 是继肿瘤、心血管疾病和中风之外危害人类健康的致死性疾病^[1],且发病率逐年上升^[2]。目前,AD的主要治疗药物有胆碱酯酶抑制剂和N-甲基-D-天冬氨酸(N-Methyl-D-aspartic acid, NMDA)拮抗剂,但这些药物都只能缓解疾病进程,无法治愈AD^[3],且迄今为止尚无安全有效的阻断AD病程进展的药物^[4]。AD的发病机制仍未明确,主要存在 β -淀粉样蛋白(β -amyloid, $A\beta$)聚集学说、Tau蛋白过度磷酸化学说、氧化应激学说、细胞凋亡学说等在内的多种假说^[5-6]。其中,淀粉样蛋白假说认为, β -分泌酶和 γ -分泌酶对APP的异常加工导致 $A\beta$ 单体产生,而这些单体聚集成斑块并分布在海马和皮质^[7]。紫云英苷(Astragalín, AST),化学名为3,5,7,4'-四羟基黄酮-3-葡萄糖(kaempferol-3-O- β -D-glucoside),是杜仲、黄芪、辣木叶、月季等多种传统药用和食用植物中的天然黄酮类化合物之一,被证实能够抗炎、抗氧化,并且具有修复受损DNA、及保护神经等作用^[8-9]。本课题组前期研究发现AST能够促进APP/PS1转基因小鼠大脑皮质内神经元自噬减轻 $A\beta$ 沉积,改善APP/PS1转基因小鼠的学习认知能力^[10-11]。但未能充分探究AST是否同时能够抑制APP/PS1转基因小鼠大脑皮质神经元的凋亡,从而共同改善病理症状。因此本实验将进一步探讨AST能否抑制AD小鼠大脑皮质神经元凋亡,改善AD小鼠的病理症状,旨在为AST能够用于临床上治疗AD提供可靠的实验依据和理论基础。

1 材料与方 法

1.1 实验动物与饲养

18只6月龄SPF级APP/PS1(APP^{swe}, PSEN1^{dE9})雄性转基因小鼠及6只同品系同月龄SPF级

C57BL/6雄性小鼠均购自广东省实验动物中心,许可证号:SCXK(粤)2018-0002。动物均饲养于SPF级屏障环境内:将AD小鼠单笼单只饲养,12h光照循环,饮水进食自由,室温(22 \pm 2)℃,相对湿度(55 \pm 5)%。广东药科大学动物护理伦理和使用委员会批准(批准使用号为:SPF2017356)并通过本实验所有动物实验操作。

1.2 主要试剂与仪器

99.02%紫云英苷(wkq20032506)购于四川省维克奇生物科技有限公司,盐酸多奈哌齐(Donepezil, DNP)(110119-84-1)购于上海源叶生物公司,DMSO(D8370)购于北京索莱宝公司,*Bax*抗体(AF1020)购于Affinity公司、*Bcl-2*抗体(26593-1-AP)、*Caspase9*抗体(10380-1-AP)及*Caspase3*(19677-1-AP)抗体均购于proteintech公司、*Cleaved-Caspase3*抗体(ab32042)、*GAPDH*抗体(ab9485)、*NeuN*抗体(ab104224)、山羊抗兔荧光二抗(ab150077)、山羊抗小鼠荧光二抗(ab150116)、HRP山羊抗兔(ab205718)均购于abcam公司、化学发光成像与分析系统Tanon-5200购于上海天能科技有限公司,光学显微镜及成像系统AX-10购于德国ZEISS生物公司。

1.3 实验动物分组及给药

实验动物适应环境一周后,随机将18只6月龄雄性的APP/PS1转基因小鼠随机分为:APP/PS1、APP/PS1+AST、APP/PS1+DNP三组,6只6月龄雄性的C57BL/6作为对照组。

将AST和DNP分别溶于50 mL/L DMSO溶液,制成40 mg/kg AST和20 mg/kg DNP溶液。APP/PS1组小鼠给予等量50 mL/L DMSO溶液,每日给药1次,连续腹腔给药1个月。

1.4 免疫荧光染色

每组随机选取3只小鼠进行免疫荧光染色。50 mL/L戊巴比妥钠麻醉小鼠,断头取脑,于多聚甲

醛溶液固定48 h,流水冲洗,组织梯度脱水、包埋、切片。选取完整的石蜡切片,烤箱60℃烘片2 h,进行常规脱蜡水合,0.1 mol/L柠檬酸盐缓冲液抗原修复20 min,含5 ml/L Triton的PBS打孔30 min,PBST摇洗,快速免疫封闭液37℃封闭20 min,分别滴加小鼠一抗*NeuN*(1:200)和兔一抗*Bax*(1:200)、兔抗*Bcl-2*(1:200)、兔抗*Caspase9*(1:200)、兔抗*Cleaved-Caspase3*(1:200),4℃孵育过夜。PBST摇洗,再分别滴加山羊抗小鼠荧光二抗(1:200)和山羊抗兔荧光二抗(1:200)烤箱37℃孵育2 h,PBST摇洗,DAPI染液染核8 min,PBST摇洗,抗荧光淬灭剂封片,光学显微镜观察并拍照。

1.5 Western blot

每组随机选取3只小鼠进行Western blot检测。50 mL/L戊巴比妥钠麻醉小鼠,断头取脑,于冰上快速分离大脑皮质组织,根据大脑皮质组织质量,按照100:1加入RIPA和PMSF裂解,冰上研磨大脑皮质组织,4℃离心,用BCA蛋白定量试剂盒测定各组蛋白浓度,制成蛋白样品。SDS-PAGE凝胶电泳,湿转将蛋白印迹转至PVDF膜,50 g/L脱脂奶粉封闭2 h,分别滴加抗体:小鼠一抗*Bax*(1:5 000)、兔一抗*Bcl-2*(1:2 000)、兔一抗*Caspase9*(1:2 000)、兔一抗*Caspase3*(1:500)、兔一抗*GAPDH*(1:10 000),4℃孵育过夜。TBST摇洗,再滴加山羊抗小鼠二抗(1:10 000)、山羊抗兔二抗(1:10 000)于摇床缓慢孵育1 h,TBST摇洗。ECL超敏发光液显影,Image J进行蛋白灰度值测定。

1.6 Tunel染色

选取完整的脑部石蜡切片,烤箱60℃烘片2 h,进行常规脱蜡水合,0.1 mol/L柠檬酸盐缓冲液组织抗原修复20 min,含50 mL/L Triton的PBS打孔30 min,PBST摇洗,快速免疫封闭液37℃封闭20 min,滴加小鼠一抗*NeuN*(1:200),4℃孵育过夜,PBST摇洗,滴加山羊抗小鼠荧光小鼠荧光二抗(1:200),烤箱37℃孵育2 h,PBST摇洗。30 mL/L H₂O₂处理10 min,PBST摇洗,Tunel染液烤箱37℃孵育90 min。PBST摇洗,DAPI染液染核8 min,PBST摇洗,抗荧光淬灭剂封片,光学显微镜观察并拍照。

1.7 统计学分析

用Graphpad Prism 8.0分析数据所有数据以均值±标准差($\bar{x} \pm s$)表示;所有定量资料满足正态分布,且通过方差齐性检验后采用单因素方差分

析(one way-ANOVA),组间两两进行比较采用Turkey法。 $P < 0.05$ 认为差异具有统计学意义。

2 结果

2.1 紫云英苷对APP/PS1小鼠大脑内皮质神经元凋亡相关蛋白表达的影响

由免疫荧光染色结果(图1-图5)可知,与Control组相比,APP/PS1组小鼠大脑皮质神经元内*Bax*($F = 59.556$, $P < 0.000 1$)、*Caspase9*($F = 24.236$, $P < 0.000 1$)、*Cleaved-Caspase3*($F = 18.259$, $P < 0.001$)阳性细胞数量均显著增加,*Bcl-2*($F = 40.162$, $P < 0.000 1$)阳性细胞数量明显减少。而经AST、DNP分别给药处理后,小鼠大脑皮质内*Bax*、*Caspase9*、*Cleaved-Caspase3*阳性细胞数量明显减少,*Bcl-2*阳性细胞数显著增多。

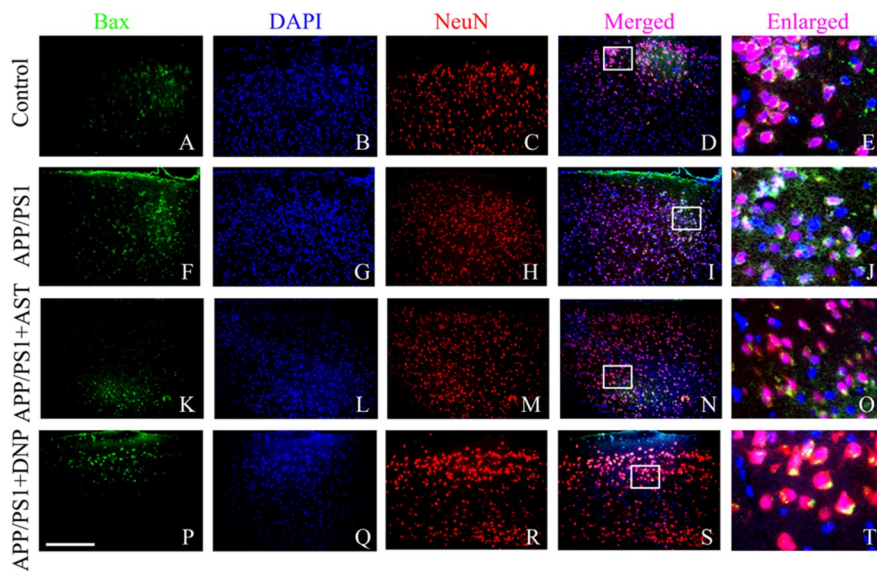
由Western blot结果(图6)显示,与Control组相比,APP/PS1组小鼠大脑皮质内神经元凋亡相关蛋白*Bax*、*Caspase9*、*Caspase3*表达水平显著上升,*Bcl-2*表达水平显著下降。而经过AST和DNP分别给药处理后,小鼠大脑皮质内神经元*Bax*($F = 3.039$, $P = 0.006$)、*Caspase9*($F = 12.272$, $P = 0.002$)、*Caspase3*($F = 37.500$, $P < 0.000 1$)的表达均出现下调,而*Bcl-2*($F = 11.171$, $P = 0.003$)表达呈上调趋势,且AST和DNP两组给药组之间差异有统计学意义。

2.2 紫云英苷对APP/PS1小鼠大脑皮质神经元凋亡的影响

由免疫荧光结果(图7)可知,与Control组相比,APP/PS1组小鼠大脑皮质内Tunel阳性神经元数量明显增多,而经AST、DNP分别给药处理后,APP/PS1小鼠大脑皮质内Tunel阳性神经元数量明显减少,且AST和DNP两组之间差异无统计学意义。

3 讨论

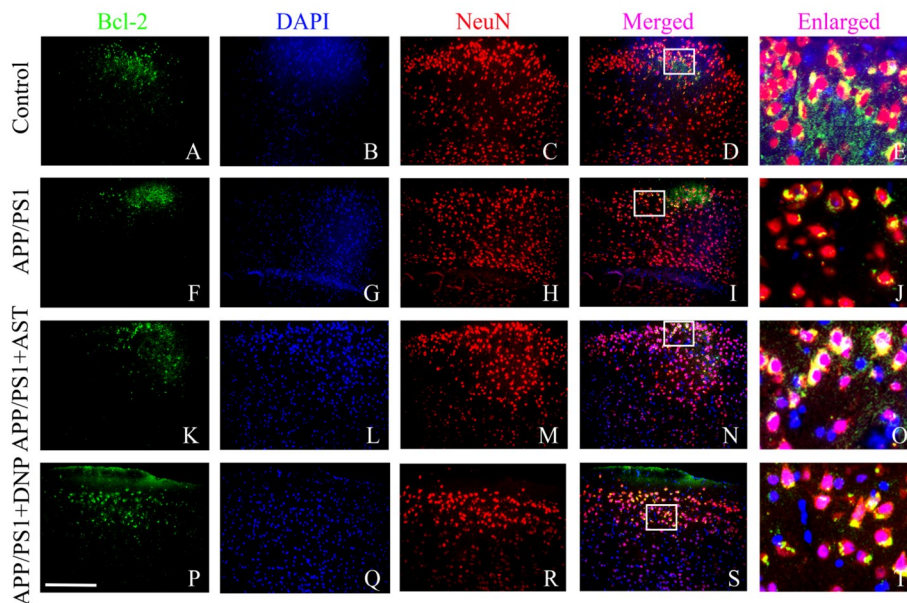
痴呆是认知能力下降的统称,而阿尔茨海默病(AD)几乎占痴呆症病例的四分之三,它严重干扰人们的日常生活^[12],因此世界卫生组织确认其为全球公共卫生优先事项^[2]。我国是世界上AD患病率最高的国家^[13],且目前临床用于治疗AD的药物



The scale shown in A-D, F-I, K-N, P-S: 100 μm . $n=3/\text{group}$.

图1 免疫荧光染色检测小鼠大脑皮质内 *Bax* 与 *NeuN* 共表达情况

Fig. 1 Multiple immunofluorescent detection of the co-expression of *Bax* and *NeuN* in the cerebral cortex of mice



The scale shown in A-D, F-I, K-N, P-S: 100 μm . $n=3/\text{group}$.

图2 免疫荧光染色检测小鼠大脑皮质内 *Bcl-2* 与 *NeuN* 共表达情况

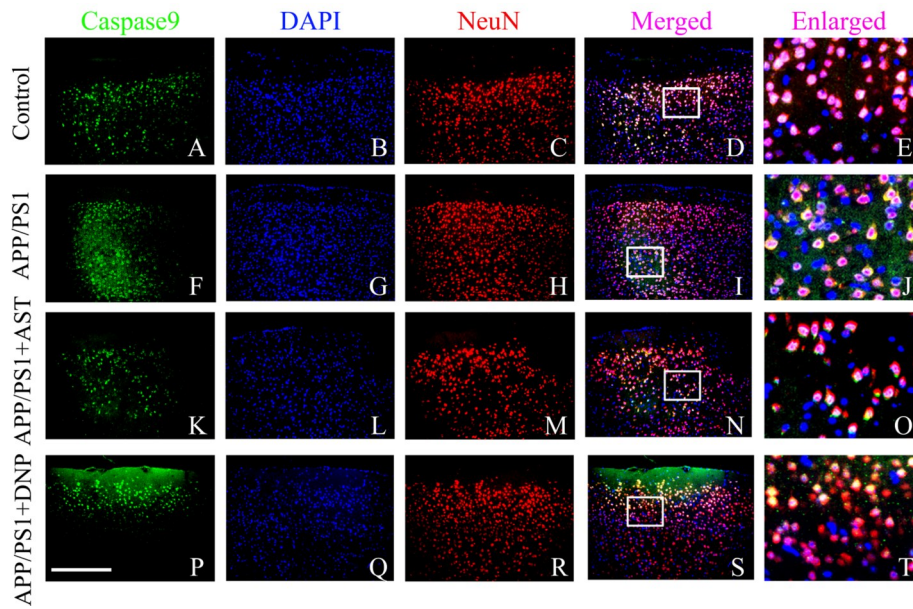
Fig. 2 Multiple immunofluorescent detection of the co-expression of *Bcl-2* and *NeuN* in the cerebral cortex of mice

只能缓解相应症状,控制病程进展^[14]。

AD的典型病理症状之一就是A β 的沉积,研究表明A β 的异常沉积会激活一系列半胱天蛋白酶来诱导神经元的凋亡,而半胱天冬酶活化和细胞凋亡,又会加剧A β 积累,从而加重AD病理症状^[15]。*Bax*可以改变线粒体膜电位,增加线粒体膜的通透性,细胞色素C释放,诱发半胱氨酸天冬氨酸酶的级联反应,导致细胞凋亡。而*Bcl-2*家族蛋白可以

抑制凋亡蛋白引发的一系列信号激活发挥抗凋亡作用^[16]。

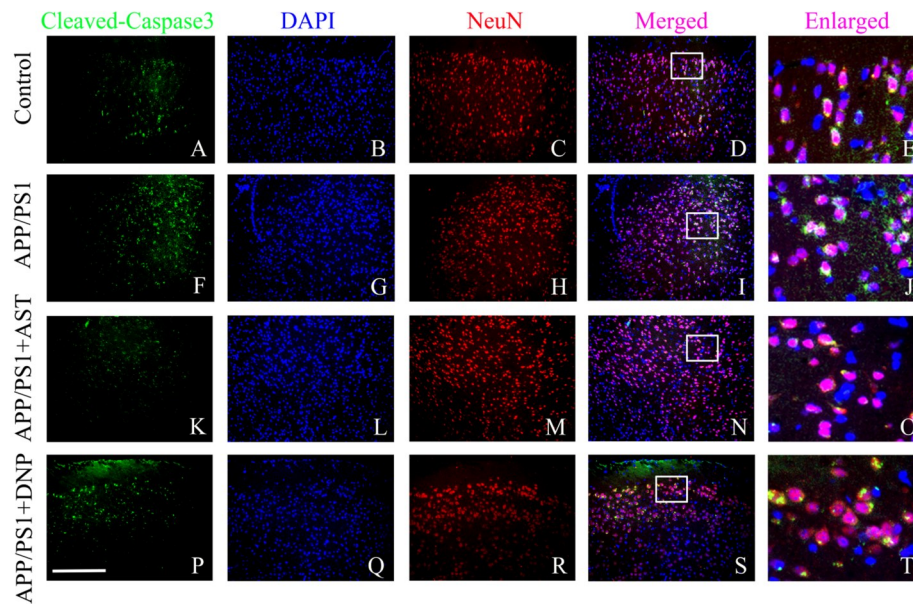
AST作为天然的黄酮类化合物,具有抗炎、保护神经等多种药理特性,且未发现存在细胞毒性。一系列研究表明,AST能够通过JAK/STAT信号通路上调DLBCL细胞中*p53*水平的表达,激活线粒体途径诱发细胞发生凋亡^[17];AST还可抑制内毒素诱导的氧化应激^[18]、抑制肝癌细胞的线粒体功



The scale shown in A-D, F-I, K-N, P-S: 100 μm. n=3/group.

图3 免疫荧光染色检测小鼠大脑皮质内 *Caspase9* 与 *NeuN* 共表达情况

Fig. 3 Multiple immunofluorescent detection of the co-expression of *Caspase9* and *NeuN* in the cerebral cortex of mice



The scale shown in A-D, F-I, K-N, P-S: 100 μm. n=3/group.

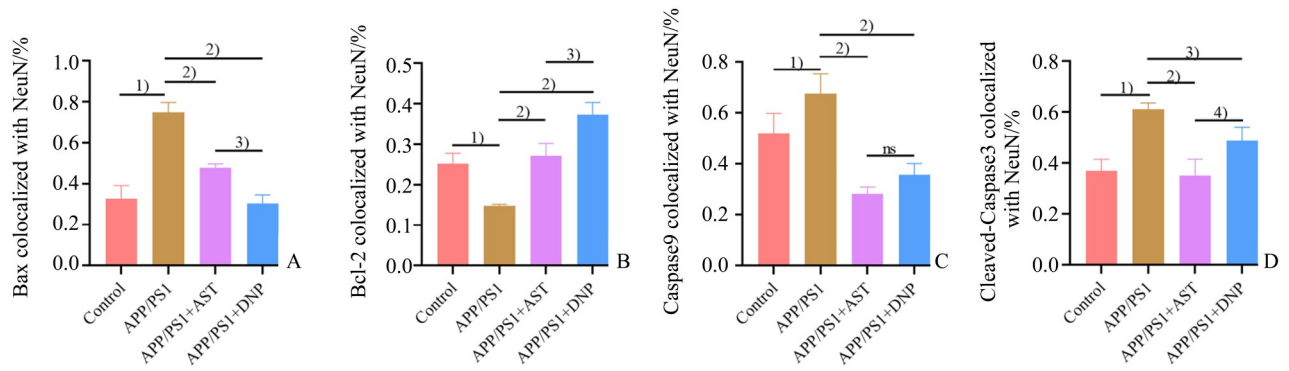
图4 免疫荧光染色检测小鼠大脑皮质内 *Cleaved-Caspase3* 与 *NeuN* 共表达情况

Fig. 4 Multiple immunofluorescent detection of the co-expression of *Cleaved-Caspase3* and *NeuN* in the cerebral cortex of mice

能,使癌细胞内 ROS 水平升高,激活一系列 caspase 酶进而促进癌细胞凋亡^[19]。

为探究 AST 抑制神经元凋亡的分子作用机制,本研究以 APP/PS1 小鼠作为 AD 动物模型展开研究,并选用 DNP 作为 AST 的阳性药物对照。我们通过 Western blot 法检测凋亡相关蛋白的表达。结

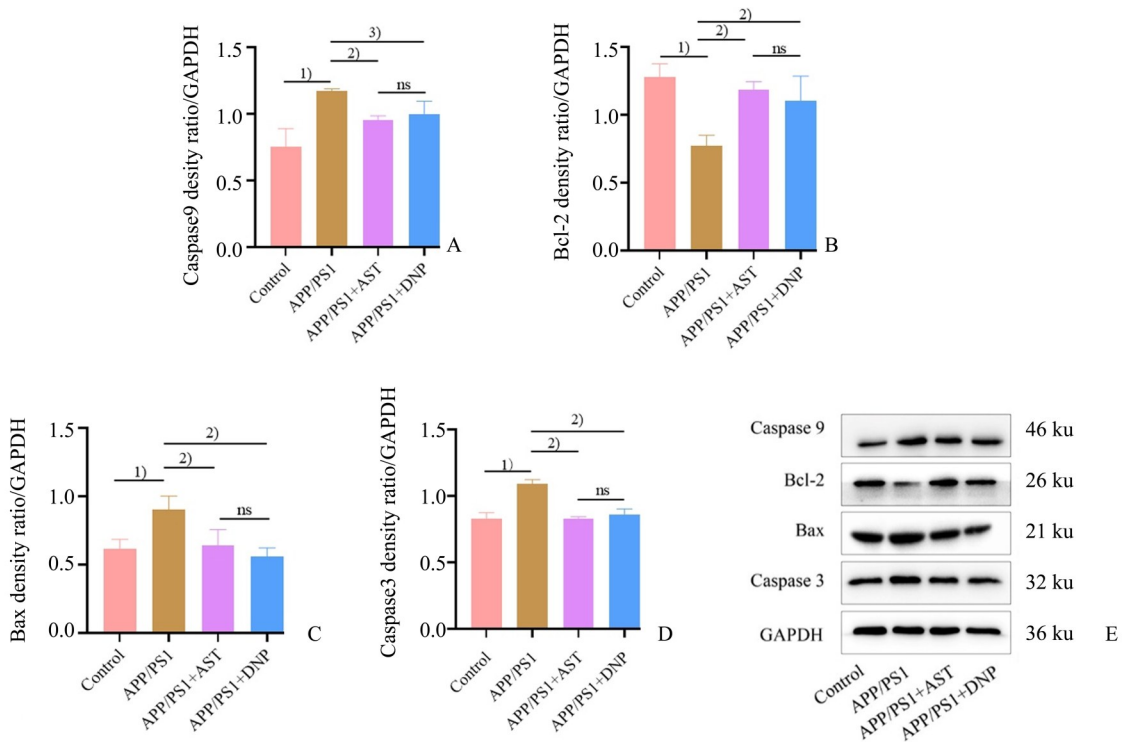
果表明,AST 能够显著增加神经元中抗凋亡的 *Bcl-2* 蛋白表达,显著降低促凋亡的 *Bax*、*Caspase9* 和 *Caspase-3* 蛋白表达。我们通过免疫荧光染色和 Tunel 染色,还发现 AST 能够显著抑制 APP/PS1 小鼠大脑皮质神经元的凋亡。这些结果提示 AST 可能通过改善 APP/PS1 小鼠大脑皮质神经元内抗凋



Proportion of colocalization of *Bax*, *Bcl-2*, *Caspase9* and *Cleaved-Caspase3* with *NeuN* in the cerebral cortex of APP/PS1 mice. $F = 59.556, P < 0.0001$; $F = 40.162, P < 0.0001$; $F = 24.236, P < 0.0001$; $F = 18.259, P = 0.001$. $n=3$ /group. 1) $P < 0.0001$ compared with Control group in A; $P < 0.005$ compared with Control group in B; $P < 0.05$ compared with Control group in C; $P < 0.001$ compared with Control group in D. 2) $P < 0.0001$ compared with APP/PS1 group in A; $P < 0.001$ compared with APP/PS1 group in B; $P < 0.0001$ compared with APP/PS1 group in C; $P < 0.001$ compared with APP/PS1 group in D. 3) $P < 0.05$ compared with the APP/PS1+AST group in A; $P < 0.005$ compared with APP/PS1+AST group in B; $P < 0.05$ compared with APP/PS1 group in D. 4) $P < 0.05$ compared with the APP/PS1+AST group in D. All the data are analyzed using one-way ANOVA of variance followed by Turkey test.

图5 APP/PS1小鼠大脑皮质内 *Bax*、*Bcl-2*、*Caspase9* 与 *Cleaved-Caspase3* 与 *NeuN* 共定位统计分析

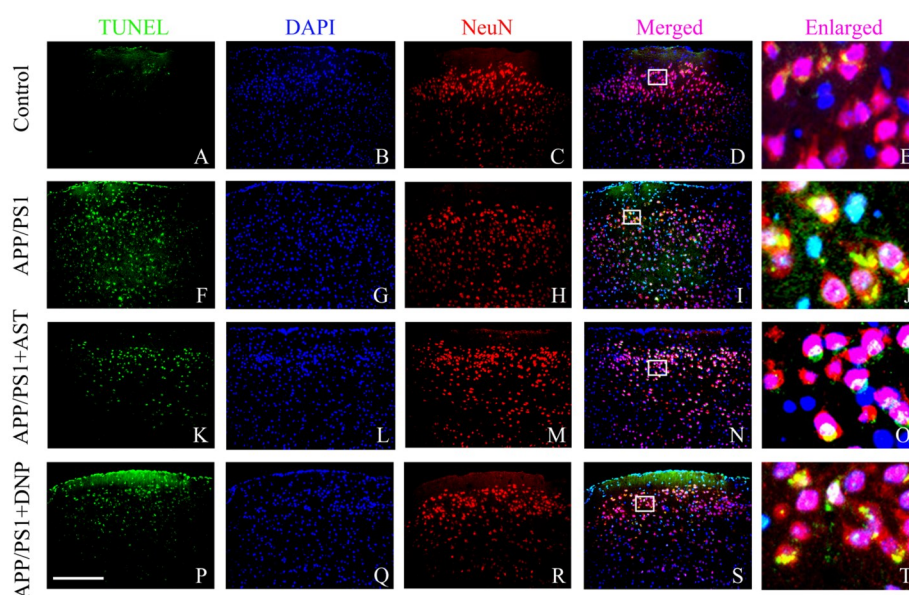
Fig. 5 Statistical Analysis of colocalization of *Bax*, *Bcl-2*, *Caspase9* and *Cleaved-Caspase3* with *NeuN* in the cerebral cortex of APP/PS1 mice



Western blot for determining the protein levels of *Caspase9*, *Bcl-2*, *Bax*, *Caspase3*. $F = 12.272, P = 0.002$; $F = 11.171, P = 0.003$; $F = 9.039, P = 0.006$; $F = 37.500, P < 0.0001$. $n=3$ /group. 1) $P < 0.005$ compared with Control group in A; $P < 0.005$ compared with Control group in B; $P < 0.05$ compared with Control group in C; $P < 0.0001$ compared with Control group in D. 2) $P < 0.05$ compared with APP/PS1 group in A; $P < 0.05$ compared with APP/PS1 group in B; $P < 0.05$ compared with APP/PS1 group in C; $P < 0.0001$ compared with APP/PS1 group in D. 3) $P < 0.05$ compared with the APP/PS1 group in A. All the data are analyzed using one-way ANOVA of variance followed by Turkey test.

图6 Western blot检测小鼠大脑皮质内 *Caspase9*、*Bcl-2*、*Bax*、*Caspase3* 的表达水平

Fig. 6 Western blot to detect the expression of *Caspase9*, *Bcl-2*, *Bax* and *Caspase3* in the cerebral cortex of mice



The scale shown in A-D, F-I, K-N, P-S: 100 μm . $n=3/\text{group}$.

图7 TUNEL检测小鼠大脑皮质内神经元凋亡情况

Fig. 7 TUNEL detection of neuronal apoptosis in the cerebral cortex of mice

亡与促凋亡蛋白的失衡来抑制神经元凋亡。

综上所述,AST能够抑制APP/PS1小鼠大脑皮质神经元凋亡,其作用机制可能与*Bcl-2*蛋白表达上调和*Bax*、*Caspae9*和*Caspase-3*蛋白表达下调有

关。本实验对AST抑制APP/PS1小鼠大脑皮质神经元凋亡的分子作用机制进行初步探讨,有望为AST在临床上治疗AD提供潜在的治疗靶点,但具体的凋亡作用机制仍待进一步的深入探讨。

参考文献

- [1] Lee W, Kim SH. Autophagy at synapses in neurodegenerative diseases[J]. Arch Pharm Res, 2019, 42(5):407-415.
- [2] Lane CA, Hardy J, Schott JM. Alzheimer's disease[J]. Eur J Neurol, 2018, 25(1):59-70.
- [3] Breijyeh Z, Karaman R. Comprehensive review on Alzheimer's disease: causes and treatment[J]. Molecules, 2020, 25(24): 5789.
- [4] 肖国民. 虾青素对阿尔茨海默病神经保护作用及其机制研究进展[J]. 健康研究, 2022, 42(5):556-558.
Xiao GM. Research progress on the neuroprotective effect of astaxanthin on Alzheimer's disease and its mechanism [J]. Health Res, 2022, 42(5):556-558.
- [5] Li Y, Zhang J, Wan J, et al. Melatonin regulates A β production/clearance balance and A β neurotoxicity: A potential therapeutic molecule for Alzheimer's disease[J]. Biomed Pharmacother, 2020, 132:110887.
- [6] 谢林江, 邓婷, 徐颖, 等. 阿尔茨海默病信号通路研究进展及对策研究[J]. 中国药理学通报, 2021, 37(2):165-170.
Xie LJ, Deng T, Xu Y, et al. Research progress and countermeasures of Alzheimer's disease signaling pathways [J]. Chinese Pharmacol Bull, 2021, 37(2):165-170.
- [7] Tiwari S, Atluri V, Kaushik A, et al. Alzheimer's disease: pathogenesis, diagnostics, and therapeutics [J]. Int J Nanomedicine, 2019, 14:5541-5554.
- [8] 张立敏, 顾超, 安红梅. 氧化应激介导的细胞凋亡在阿尔茨海默病中的作用[J]. 医学综述, 2021, 27(9):1685-1690.
Zhang L, Gu C, An HM. Role of oxidative stress-mediated apoptosis in Alzheimer's disease[J]. Med Recapitulate, 2021, 27(9):1685-1690.
- [9] 陈世春, 徐永祥, 韩伟超, 等. 紫云英苷的药理特性及其作用机制研究进展[J]. 中华中医药学刊, 2022, 40(11): 118-123; +287.
Chen SC, Xu YX, Han WC, et al. Research progress on the pharmacological properties and mechanism of Astragaloside [J]. Chin Archives of Tradit Chin Med, 2022, 40(11): 118-123; +287.
- [10] Yang CZ, Wang SH, Zhang RH, et al. Neuroprotective effect of astragaloside via activating PI3K/Akt-mTOR-mediated autophagy on APP/PS1 mice [J]. Cell Death Discov, 2023, 9(1):15.

- [11] 杨翠珠,张润恒,王姝涵,等.紫云英苷诱导自噬减轻APP/PS1转基因小鼠皮质内神经元损伤及老年斑沉积[J].中山大学学报(医学科学版),2022,43(2):238-246.
Yang CZ, Zhang RH, Wang SH, et al. Astragaloside alleviates neuronal damage and senile plaque deposition via activating autophagy in the cortex of APP/PS1 transgenic mice[J]. J Sun Yat-sen University (Med Sci), 2022, 43(2):238-246.
- [12] Briggs R, Kennelly SP, O'Neill D. Drug treatments in Alzheimer's disease [J]. Clin Med (Lond), 2016, 16(3): 247-53.
- [13] 李光美,王朝群,唐超,等.天麻多糖对阿尔茨海默症小鼠焦虑行为及记忆功能的影响[J].遵义医科大学学报,2023,46(3): 227-233;+285.
Li GM, Wang CQ, Tang C, et al. Effect of Gastrodia elata polysaccharide on anxiety-like and learning/memory behavior in AD mouse models[J]. J Zunyi Med Univ, 2023, 46(3): 227-233;+285.
- [14] Xu X, Lai Y, Hua ZC. Apoptosis and apoptotic body: disease message and therapeutic target potentials [J]. Biosci Rep, 2019, 39(1):BSR20180992.
- [15] 李晓敏,肖锋,靳纷纷,等.神经节苷脂GM1对A β ₁₋₄₂诱导的AD小鼠学习记忆能力及神经细胞凋亡的影响[J].沈阳药科大学学报,2019,36(7):612-616.
Li XM, Xiao F, Jin FF, et al. The effect of gangliosides GM1 on learning and memory ability and neuronal apoptosis in AD mice induced by A β ₁₋₄₂[J]. J Shenyang Pharmaceutical University, 2019, 36(7):612-616.
- [16] 李利娟,刘文涛,罗欢欢,等.菟丝子总黄酮对小鼠睾丸间质细胞凋亡相关蛋白Bax、Bcl-2、Caspase-3的影响[J].解放军医学院学报,2022,43(2):199-204.
Li LJ, Liu WT, Luo HH, et al. Effects of total flavonoids from Semen Cuscuta on apoptosis related proteins Bax, Bcl-2 and Caspase-3 of mouse testicular Leydig cells [J]. Acad J Chin PLA Med Sch, 2022, 43(2):199-204.
- [17] 王瑜,朱明了,何施燕,等.紫云英苷诱导DLBCL细胞系OCI-LY8凋亡[J].中国病理生理杂志,2021,37(5): 885-890.
Wang Y, Zhu ML, He SY, et al. Astragaloside induces apoptosis of DLBCL cell line OCI-LY8[J]. Chin J Physiol, 2021, 37(5):885-890.
- [18] 聂龙,彭磊,李钰芳,等.紫云英苷生物活性及其机制的研究进展[J].热带农业科学,2020,40(6):64-70.
Nie L, Peng L, Li YF, et al. Research Advances in the Biological Activities and Mechanism of Astragaloside [J]. Chin J Trop Agric, 2020, 40(6):64-70.
- [19] 张翼.紫云英苷诱导人胃癌细胞凋亡、周期阻滞及迁移抑制作用的分子机制研究[D].黑龙江八一农垦大学,2020.
Zhang Y. Molecular mechanism of astragaloside induced apoptosis, cell cycle arrest and migration inhibition in human gastric cancer cells [D]. Heilongjiang Bayi Agricultural University, 2020.

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