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内脂素对老年大鼠脑组织损伤和炎症反应的影响分析*

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摘要 目的:探讨与分析内脂素对老年大鼠脑组织损伤和炎症反应的影响。**方法:**10 个月龄老年健康雄性 Sprague-Dawley(SD)大鼠 60 只随机平分为两组 - 对照组与内脂素组,内脂素组给予腹腔注射重组人内脂素 200 μg /次,对照组均给予等量蒸馏水灌胃,2 次/w,连续给药 4 w。对比两组给药前、给药第 2 w、给药第 4 w 的逃避潜伏期、血清白介素(IL)-6 与 C-反应蛋白(C-reactive protein, CRP)含量,及给药第 4 w 的线粒体超氧化物歧化酶(Superoxide dismutase, SOD)与谷胱甘肽过氧化物酶(Glutathione peroxidase, GSH-Px)活性、海马与皮层区神经元凋亡率。**结果:**所有大鼠在实验期间均出现典型的绕池壁现象。两组给药前逃避潜伏期、血清 IL-6 与 CRP 含量对比差异无统计学意义($P>0.05$),给药后两组第 2 w、给药第 4 w 的逃避潜伏期、血清 IL-6 与 CRP 含量均降低($P<0.05$),且内脂素组给药第 2 w、给药第 4 w 的上述指标低于对照组,对比均有统计学意义($P<0.05$);内脂素组给药第 4 w 的线粒体 SOD、GSH-Px 活性高于对照组,海马与皮层区神经元凋亡率低于对照组,经对比差异有统计学意义($P<0.05$)。**结论:**内脂素在老年大鼠的应用能缓解脑组织损伤,抑制炎症反应,有利于清除过量的自由基,降低神经元的凋亡率。

关键词:内脂素;老年大鼠;脑组织损伤;炎症反应;神经元

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Analysis of the Effect of Visfatin on Brain Damage and Inflammation in Aged Rats*

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ABSTRACT Objective: To explore and analyze the effect of visfatin on brain damage and inflammation in aged rats. **Methods:** 60 cases of 10-month-old healthy male Sprague-Dawley (SD) rats were equally randomly divided into two groups-the control group and the visfatin group. The visfatin group were given intraperitoneal injection of recombinant human visfatin 200 μg /time, the control group were given equal amount of distilled water by gavage, 2 times/week for 4 consecutive weeks. The escape latency, serum interleukin (IL)-6 and C-reactive protein (C-reactive protein, CRP) levels before administration, the 2nd week of administration, and the 4th week of administration were compared between the two groups. 4 weeks of mitochondrial superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) activity, hippocampal and cortical neuronal apoptosis rate. **Results:** All rats were showed typical phenomenon around the pool wall during the experiment. There was no significant difference in the escape latency, serum IL-6 and CRP content between the two groups before administration ($P>0.05$). The escape latency, serum IL-6 and serum IL-6 and CRP levels in the 2nd week and 4th week after administration The content of CRP was reduced ($P<0.05$), and the above indicators of the visfatin group were lower than those of the control group on the second and fourth weeks of administration, and the comparison was statistically significant ($P<0.05$); the visfatin group Mitochondrial SOD and GSH-Px activities were higher than those in the control group on the 4th week of administration, and the apoptosis rate of neurons in the hippocampus and cortex was lower than that in the control group. The difference was statistically significant ($P<0.05$). **Conclusion:** The application of visfatin in aged rats can alleviate brain tissue damage, inhibit inflammatory response, help to remove excess free radicals, and reduce neuronal apoptosis rate.

Key words: Visfatin; Aged rats; Brain tissue injury; Inflammation; Neurons

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前言

老年人多伴有神经元损伤与认知功能障碍,特别是老龄化导致的细胞凋亡在神经元损伤过程中发挥重要作用,也与神经系统的完整性具有相关性^[1,2]。在颅内脑组织中,海马组织是学习、记忆等高级神经活动的重要部位,老年患者的海马组织伴有退化情况,可导致集体学习、记忆功能障碍^[3,4]。内脂素(Visfatin)是一种脂肪细胞因子,可在内脏脂肪中大量表达,具有改善胰岛素抵抗和抗糖尿病作用,从而有可能在神经系统的发育、损伤和修复过程发挥重要作用^[5,7]。细胞学研究也显示内脂素具有重要的抗氧化活性,增强机体细胞免疫功能,有助于保护细胞膜结构和功能完整性,清除过量的自由基,从而发挥抗衰老的作用^[8,9]。不过也有离体实验结果表明,内脂素可增强体外培养的神经元细胞的寡聚化反应和细胞毒性,导致细胞凋亡^[10,11]。基于以上理由,本研究探讨了内脂素对老年大鼠脑组织损伤和炎症反应的影响,希望为临床工作中的用药提供参考依据。现总结报道如下。

1 材料与方法

1.1 研究材料

本研究经本院动物伦理委员会批准,10个月龄老年无特定病原体(Specific pathogen Free,SPF)级健康雄性Sprague-Dawley (SD)大鼠60只由实验动物中心提供(体重520~550 g,许可证号:SCXK2020-11113,质量合格证号:00024362,购买于辽宁长生生物技术有限公司)。整个实验过程中充分保障实验动物福利,大鼠均自由摄食和饮水,12 h:12 h照明,室温 $22\pm 2^{\circ}\text{C}$,通风良好,环境安静。

ZH0065 Morris水迷宫视频分析系统型号(北京硕林苑科技有限公司)、重组人内脂素(上海研卉生物科技有限公司,批号10110334)、炎症因子检测试剂盒(扬子江药业集团有限公司,批号13032221)、线粒体氧化应激检测试剂盒(Cusabio公司,批号20194924)。

1.2 动物分组与处理

将60只大鼠随机随机平分为两组-对照组与内脂素组。实验前将SD大鼠在动物中心饲养1 w,实验前12 h禁饮食。内脂素组给予腹腔注射重组人内脂素 $200\ \mu\text{g}/\text{次}$, $2\ \text{次}/\text{w}$ 。对照组均给予等量蒸馏水灌胃,连续给药4 w。两组大鼠均按标准大鼠饲料饲养。

1.3 观察指标

(1)Morris水迷宫实验:在给药前、给药第2 w、给药第4 w记录大鼠在120 s内水中游泳的时间和运动轨迹,大鼠从放入水池到找到平台的时间记为逃避潜伏期,如果超过120 s仍未找到平台,逃避潜伏期记为120 s;如果找到平台后爬上平台并5 s以上,则认为找到平台。(2)取上述时间点的大鼠血液学样本,分离血清后,采用酶联免疫法检测白介素(Interleukin,IL)-6与C-反应蛋白(C-reactive protein,CRP)含量。(3)给药第4 w处死大鼠,迅速打开颅腔取出大脑,差速离心提取脑组织线粒体,采用放射免疫法检测超氧化物歧化酶(Superoxide dismutase,SOD)与谷胱甘肽过氧化物酶(Glutathione peroxidase,GSH-Px)活性。(4)取大鼠的海马与皮层区组织,制成病理切片,切片分别经过过氧化氢、复合消化液、地高辛标记处理后,连接生物素化抗地高辛抗体,染色后在光镜下观察海马与皮层区神经元,计数凋亡细胞,计算神经元凋亡率。

1.4 统计方法

选择SPSS 25.0软件,计量数据采用均数 \pm 标准差($\bar{x}\pm s$)表示,对比方法为t检验或者方差分析,以 $P<0.05$ 为有统计学意义。

2 结果

2.1 逃避潜伏期对比

所有大鼠在实验期间均出现典型的绕池壁现象。两组给药前逃避潜伏期对比差异无统计学意义($P>0.05$),给药后两组第2 w、给药第4 w的逃避潜伏期均降低($P<0.05$),且内脂素组给药第2 w、给药第4 w的逃避潜伏期低于对照组,对比均有统计学意义($P<0.05$),见表1。

表1 两组不同时间点的逃避潜伏期对比($s,\bar{x}\pm s$)

Table 1 Comparison of escape latency between the two groups at different time points ($s,\bar{x}\pm s$)

Groups	n	Before administration	2 w of administration	4 w of administration
Visfatin group	30	118.09 \pm 11.23	75.87 \pm 18.23 ^{#*}	55.32 \pm 7.45 ^{#*}
Control group	30	118.34 \pm 19.93	114.88 \pm 20.34 [#]	112.22 \pm 8.41 [#]

Note: compare with the before administration, [#] $P<0.05$; compare with the control group, * $P<0.05$.

2.2 血清IL-6与CRP含量对比

两组给药前血清IL-6与CRP含量对比差异无统计学意义($P>0.05$),两组给药第2 w、给药第4 w的血清IL-6与CRP含量也低于给药前($P<0.05$),且内脂素组给药第2 w、给药第4 w的血清IL-6与CRP含量低于对照组,经对比差异有统计学意义($P<0.05$),见表2。

2.3 线粒体SOD、GSH-Px活性对比

内脂素组给药第4 w的线粒体SOD、GSH-Px活性高于对照组,经对比差异有统计学意义($P<0.05$),见表3。

2.4 神经元凋亡率对比

内脂素组给药第4 w的海马与皮层区神经元凋亡率低于对照组,经对比差异有统计学意义($P<0.05$),见表4。

3 讨论

老年人可表现为认知功能和记忆能力下降,特别是组织器官的老化可导致应激毒性副产物的蓄积,相应的大脑神经元也减少,使得大脑的应激能力下降^[12,13]。特别是神经组织器官老化影响脑内神经元及突触结构和功能的可塑性,减少了海马内神

表 2 两组不同时间点的血清 IL-6 与 CRP 含量对比($\bar{x} \pm s$)

Table 2 Comparison of serum IL-6 and CRP levels at different time points between the two groups ($\bar{x} \pm s$)

Groups	n	IL-6(pg/mL)			CRP(mg/L)		
		Before administration	2 w of administration	4 w of administration	Before administration	2 w of administration	4 w of administration
Visfatin group	30	23.59± 1.82	10.38± 1.47 ^{#*}	5.87± 0.32 ^{#*}	17.87± 1.47	9.27± 0.38 ^{#*}	5.09± 0.14 ^{#*}
Control group	30	23.33± 2.22	24.01± 3.18 [#]	24.98± 2.17 [#]	17.20± 1.22	17.98± 1.37 [#]	18.00± 0.87 [#]

Note: compare with the before administration, [#]*P*<0.05; compare with the control group, **P*<0.05.

表 3 两组给药第 4 周的线粒体 SOD、GSH-Px 活性对比(U/mg, $\bar{x} \pm s$)

Table 3 Comparison of mitochondrial SOD and GSH-Px activities in the 4th week of the two groups (U/mg, $\bar{x} \pm s$)

Groups	n	SOD	GSH-Px
Visfatin group	30	32.98± 3.33*	49.87± 5.69*
Control group	30	18.99± 2.09	27.98± 3.12

Note: compare with the control group, **P*<0.05.

表 4 两组给药第 4 周的海马与皮层区神经元凋亡率对比(% , $\bar{x} \pm s$)

Table 4 Comparison of the apoptosis rate of hippocampus and cortical neurons in the 4th week of the two groups (% , $\bar{x} \pm s$)

Groups	n	Hippocampi	Cortical area
Visfatin group	30	2.45± 0.13*	3.10± 0.22*
Control group	30	8.47± 1.24	10.73± 1.47

Note: compare with the control group, **P*<0.05.

经生成,造成 IL-6 与 CRP 大量释放到血中,进一步造成神经行为功能的损伤^[14]。内脂素是一种新型的脂肪因子,是在有活性的外周血淋巴细胞中分离出来的蛋白质,主要由内脏脂肪组织产生,已与多种细胞过程相关,并且是细胞凋亡和存活的重要因素^[15,16]。内脂素具有类胰岛素样作用,位于染色体 7q22.1,包含 10 个内含子和 11 个外显子,具有调节血管平滑肌的成熟、参与动脉粥样硬化的形成、促进脂肪的积聚和合成等多种功能^[17]。Morris 水迷宫实验是目前比较公认的评价啮齿类动物学习记忆的一种实验手段。本研究显示所有老年大鼠在学习记忆功能测试的前期均出现典型的绕池壁现象,但随着游泳次数增多和引导平台练习,大鼠的逃避潜伏期缩短。与吴毅^[18]等人的研究的类似,该学者探究了内脂素改善创伤性脑损伤小鼠神经功能修复的研究,结果显示内脂素治疗组小鼠水迷宫潜伏逃避期小于对照组。内脂素治疗组小鼠脑切片中 TUNEL 阳性细胞数小于对照组。本研究显示内脂素组给药第 2 w、给药第 4 w 的逃避潜伏期、血清 IL-6 与 CRP 低于对照组,也低于给药前,与 Ke Xiao^[19]的研究类似,该学者等研究内脂素是否参与大鼠脂多糖诱导的炎症或细胞凋亡,结果显示内脂素可以调节大鼠脾脏的抗炎细胞因子和促炎细胞因子,如 IL-10、IL-4、IL-6、TNF- α 和 IL-1 β ,表明内脂素在老年大鼠的应用能减轻脑组织损伤,抑制炎症反应的发生。当前基础研究也显示内脂素能激活 NF- κ B 信号通路与 p38 信号通路,参与机体免疫调节作用^[20,21]。

脑组织老化后海马神经元可能发生延迟性死亡,导致长期认知功能障碍,可表现为 SOD、GSH-Px 活性降低,机体糖代谢能力衰退^[22,23]。本研究显示内脂素组给药第 4 w 的线粒体 SOD、GSH-Px 活性高于对照组,与 Rafał Jakub Bułdak^[24]等学者的研究类似,该学者研究内脂素影响 Me45 人恶性黑色素瘤细胞中

的氧化还原适应性反应和增殖,结果显示内脂素增加了 Me45 人恶性黑色素瘤细胞培养上清液中所选抗氧化酶(SOD、CAT、GSH-Px)的活性,表明内脂素会触发氧化还原适应反应,从而导致 Me45 黑色素瘤细胞中抗氧化能力的上调以及脂质过氧化过程的水平降低。从机制上分析,内脂素具有重要的抗氧化活性,可促使大脑神经信号传导加快,有利于清除过量的自由基^[25,26];并且其能加快机体能量代谢的速率,保护细胞膜结构和功能完整性,从而发挥抗衰老的作用^[27,28]。

大脑皮层区和海马是学习记忆的关键部位,大脑额叶皮层、颞叶皮层损伤时认知功能减退^[29,30]。大鼠海马区的锥体细胞对缺血性损伤很敏感,缺血和创伤应激可造成海马区的神经元损伤,使得空间学习和记忆能力下降^[31,32]。本研究显示内脂素组给药第 4 w 的海马与皮层区神经元凋亡率低于对照组。与 Erfani S^[33]的研究类似,该学者探究了内脂素抑制大鼠短暂性全脑缺血/再灌注后海马 CA3 细胞的凋亡和坏死,结果表明,与缺血组相比,内脂素治疗可显著降低海马 CA3 区的细胞凋亡和坏死细胞死亡,说明内脂素治疗可通过预防神经元坏死和凋亡减少脑缺血后海马 CA3 损伤。从机制上分析,内脂素对正常脑皮质神经元有维持存活效应,可通过提高脂肪组织葡萄糖摄取能力,调节糖代谢,从而降低海马与皮层区神经元凋亡率^[34,35]。本研究也存在一定的不足,神经行为学改变能够在部分程度上反映大鼠脑组织损伤功能的变化,但是无法进行全面反映,且纳入指标比较少,将在后续研究中深入探讨。

总之,内脂素在老年大鼠的应用能缓解脑组织损伤,抑制炎症反应,有利于清除过量的自由基,降低神经元的凋亡率。

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