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超声重复辐照孕鼠对子代海马 NMDA 神经损伤的影响 *

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摘要 目的：探讨超声重复辐照孕鼠对子代海马 N- 甲基 -D 天冬氨酸(N-methyl-D aspartic acid，NMDA)神经损伤的影响。**方法：**孕 12~14 d 昆明种小鼠 27 只随机平分为三组 - 对照组、短时间辐照组、长时间辐照组。用超声探头在各组孕鼠进行辐照 0 min、10 min 与 20 min，让母鼠自然分娩哺育幼仔，将各组仔鼠随机挑选 12 只，检测仔鼠海马组织 NMDA 表达与神经损伤情况。**结果：**辐照过程中无孕鼠死亡，短时间辐照组、长时间辐照组仔鼠第 30 d 与 60 d 的总路程、中央路程、中央时间都少于对照组(P<0.05)，长时间辐照组低于短时间辐照组(P<0.05)。短时间辐照组、长时间辐照组仔鼠第 60 d 的神经元细胞凋亡指数、海马组织乙酰胆碱酯酶含量都高于对照组(P<0.05)，NMDA 蛋白相对表达水平低于对照组(P<0.05)，长时间辐照组与短时间辐照组对比差异也都有统计学意义(P<0.05)。**结论：**超声重复辐照孕鼠能抑制仔鼠海马组织 NMDA 蛋白表达，促进神经元细胞凋亡与提高乙酰胆碱酯酶含量，从而降低仔鼠的自主记忆活动能力。

关键词：超声重复辐照；孕鼠；仔鼠；海马组织；N- 甲基 -D 天冬氨酸

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Effects of Repeated Ultrasound Irradiation of Pregnant Rats on the Hippocampal NMDA Nerve Injury of Offspring*

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ABSTRACT Objective: To investigate the effects of repeated ultrasound irradiation of pregnant rats on the offspring's hippocampal N-methyl-D aspartic acid (NMDA) nerve damage. **Methods:** 27 cases of Kunming mice of 12-14 days gestation were randomly equally divided into three groups-control group, short-term irradiation group and long-term irradiation group. The cases in each group were irradiated with Repeated Ultrasound Irradiation for 0 min, 10 min and 20 min. The mother mice were allowed to give birth to their pups naturally, the offspring were randomly reduced by 12 cases in each groups, and were to detect the expression of NMDA and nerve damage in the hippocampus of the offspring. **Results:** There were no pregnant mice died during the irradiation. The total distance, central distance and central time of the offspring on the 30 th and 60 th day of the short-term and long-term radiation groups were less than those of the control group (P<0.05), the irradiation group were lower than the short-term irradiation group(P<0.05). The neuronal apoptosis index and hippocampal acetylcholinesterase content of the short-term irradiation group and the long-term irradiation group on the 60 th day were higher than those of the control group (P<0.05), and the relative expression level of NMDA protein were lower than that of the control group (P<0.05), the difference compared between the long-term irradiation group and the short-term irradiation group were also statistically significant (P<0.05). **Conclusion:** Repeated ultrasound irradiation of pregnant mice can inhibit the expression of NMDA protein in hippocampus of offspring, promote neuronal cell apoptosis and increase the content of acetylcholinesterase, thereby reduce the ability of autonomous memory of offspring.

Key words: Repeated ultrasound irradiation; Pregnant mice; Offspring mice; Hippocampal tissue; N-methyl-D aspartic acid

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前言

随着医学技术的发展，超声诊断已普遍用于临床，在多种疾病的诊断中发挥了重要作用。不过超声作为一种机械振动能量的传播形式，在发挥机械、空化、热化等效应后，还可对胚胎组织产生某些结构、生化、免疫、功能上的影响[1,2]。孕期是胎儿发育的关键期，各种不利因素均可能导致胎儿出生后的质量下降，而超声安全性也是关系到优生优育以及社会可持续发展的

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重要问题[3,4]。有研究显示长期多剂量超声可能对胎鼠发育有一定的影响，早期妊娠多次接收超声辐照，可导致胎儿的出生体重增加，但是中、晚孕期妊娠累积多次接收超声辐照，却不影响胎儿的出生体重[5,6]。还有研究认为长期超声辐照能够诱导人早孕绒毛组织细胞凋亡，导致孕鼠神经组织发生形态学改变[7]，但是具体的作用机制还不明确。在神经元发育过程中，N- 甲基 -D 天冬氨酸(N-methyl-D aspartic acid，NMDA)受体亚单位随着神经元发育及活动依赖性转变。NMDA 受体主要由 NR1/NR2B 亚基构成，海马组织的 NR1/NR2B 表达水平比例会随个体发育而升高，从而可能参与调节脑发育和突触可塑性的形成[8-10]。本文具体探讨了超声重复辐照孕鼠对子代海马 NMDA 神经损伤的影响，以明确超声重复辐照的负面作用效果与机制，现总结报道如下。

1 资料与方法

1.1 研究材料

孕 12~14 d 昆明种小鼠 27 只由本校实验动物中心提供，抗 NMDA 抗体购自美国 sigma 公司，凋亡检测试剂盒购自上海生工公司，乙酰胆碱酯酶酶联免疫检测试剂盒购自武汉三鹰公司，Photometer plus 核酸蛋白测定仪购自英国 CSL 公司。所有动物实验都遵守伦理学原则，研究也得到了医学伦理委员会的批准，自由饮食，单笼饲养，12 h:12 h 光照，饲养温度为(23±2)℃。

辐照超声设备采用 DU8 型彩色超声诊断仪(百胜公司)，配有腹部凸阵探头。

1.2 动物分组与处理

将所有孕鼠随机平分为三组 - 对照组、短时间辐照组、长时间辐照组。1 %戊巴比妥钠(剂量 30 mg/kg)腹腔注射麻醉，麻醉满意后，采用特制的木板支架，将三组孕鼠仰卧固定于木板上，下腹部浸透耦合剂，用超声探头在下腹部按进行辐照 0 min、10 min 与 20 min，辐照参数：探头频率 2.0 MHz，机械指数 1.6，热指数 1.8。让母鼠自然分娩哺育幼仔，在分娩后第 3 d，将各组仔鼠随机挑选 12 只。

1.3 观察指标

(1)待仔鼠生长到 30 d 与 60 d 时，通过开场实验通过测试仔鼠对陌生环境的自发活动参数，包括总路程、中央路程、中央时间等。(2)待仔鼠生长至 60 d，处死仔鼠，取出的新鲜脑组织标本，研磨后在流式细胞仪上检测神经元细胞的凋亡指数。(3)取仔鼠的海马组织，海马位于大脑皮层组织的外侧缘，形状为一圆的长形结构，采用酶联免疫法检测海马组织中乙酰胆碱酯酶活性。(4)取仔鼠的海马组织，冰浴下加入 100 μL 预冷的细胞裂解液匀浆，静置 30 min 后，4℃下 12000 r/min 离心 25 min 取上清，按每孔 8 %分离胶与 6 %浓缩胶加入蛋白样本 20 μg，跑 SDS-PAGE 胶后，转膜到硝酸纤维素膜上，常规室温封闭 1 h 后，分别加入单克隆兔抗大鼠 NMDA 和小鼠抗大鼠β-actin 单抗，4℃摇床孵育过夜，洗涤 3 次后加入二抗，室温孵育 1 h 后，洗涤 3 次进行曝光，计算目的蛋白的相对表达水平。

1.4 统计方法

对本研究的所有数据采用 SPSS 25.00 软件进行分析，正态分布计量资料以均数± 标准差表示 (对比为 t 检验或单因素方差分析)，计数数据以百分比表示(对比为卡方分析或单因素方差分析)，P<0.05 有统计学意义。

2 结果

2.1 仔鼠自发活动参数对比

辐照过程中无孕鼠死亡，短时间辐照组、长时间辐照组仔鼠第 30 d 与 60 d 的总路程、中央路程、中央时间都少于对照组(P<0.05)，长时间辐照组低于短时间辐照组(P<0.05)，见表 1。

表 1 三组仔鼠不同时间点的自发活动参数对比($\bar{x}\pm s$)

Table 1 Comparison of spontaneous activity parameters of three groups of offspring at different time points ($\bar{x}\pm s$)

Groups	n	30 d			60 d		
		Total distance (mm)	Central distance (mm)	Central time (s)	Total distance (mm)	Central distance (mm)	Central time (s)
Short-time irradiation group	12	10467.09±256.20#	1022.87±186.78#	56.98± 9.18#	11489.58±302.88#	1233.88±200.75#	61.75± 5.79#
Long-time irradiation group	12	9872.87±189.77#*	982.09±111.74#*	65.09± 10.66#*	10897.67±67.22#*	1098.77±199.96#*	69.09± 6.78#*
Control group	12	12302.44±645.20	1255.98±213.02	74.09± 11.48	14222.08±345.18	1432.76±178.47	79.01± 8.22
F		78.013	89.102	15.033	98.011	101.39	18.833
P		0.000	0.000	0.000	0.000	0.000	0.000

Note: Compared with the control group, #P<0.05; compared with the short-term irradiation group, *P<0.05.

2.2 神经元细胞凋亡指数对比

短时间辐照组、长时间辐照组仔鼠第 60 d 的神经元细胞凋亡指数都高于对照组(P<0.05)，长时间辐照组高于短时间辐照组(P<0.05)，见表 2。

2.3 乙酰胆碱酯酶含量对比

短时间辐照组、长时间辐照组仔鼠第 60 d 的海马组织乙酰胆碱酯酶含量高于对照组，长时间辐照组高于短时间辐照组(P<0.05)，见表 3。

2.4 NMDA 蛋白相对表达水平对比

短时间辐照组、长时间辐照组仔鼠第 60 d 的海马组织 NMDA 蛋白相对表达水平低于对照组，长时间辐照组低于短时间辐照组(P<0.05)，见表 4。

表 2 三组仔鼠神经元细胞凋亡指数对比(%, $\bar{x}\pm s$)

Table 2 Comparison of neuronal apoptosis index of three groups of offspring (%, $\bar{x}\pm s$)

Groups	n	Apoptotic index
Short-time irradiation group	12	3.11± 0.18#
Long-time irradiation group	12	5.22± 0.38#*
Control group	12	0.89± 0.12
F		21.555
P		0.000

Note: Compared with the control group, #$P<0.05$; compared with the short-term irradiation group, *$P<0.05$.

表 3 三组仔鼠海马组织乙酰胆碱酯酶含量对比(U/mgprot, $\bar{x}\pm s$)

Table 3 Comparison of acetylcholinesterase content in hippocampal tissues of three groups of offspring (U/mgprot, $\bar{x}\pm s$)

Groups	n	Acetylcholinesterase content
Short-time irradiation group	12	5.69± 0.88#
Long-time irradiation group	12	10.89± 1.38#*
Control group	12	1.76± 0.21
F		37.184
P		0.000

Note: Compared with the control group, #$P<0.05$; compared with the short-term irradiation group, *$P<0.05$.

表 4 三组仔鼠海马组织 NMDA 蛋白相对表达水平对比($\bar{x}\pm s$)

Table 4 Comparison of relative expression levels of NMDA protein in hippocampus of three groups($\bar{x}\pm s$)

Groups	n	NMDA protein
Short-time irradiation group	12	2.18± 0.33#
Long-time irradiation group	12	0.92± 0.15#*
Control group	12	6.02± 0.87
F		28.576
P		0.000

Note: Compared with the control group, #$P<0.05$; compared with the short-term irradiation group, *$P<0.05$.

3 讨论

随着超声技术的发展，超声已经广泛应用于产妇早孕、中孕、晚孕的监测，也取得了很好的成效[11,12]。由于孕期超声检查的时间越来越早，检查次数越来越多，也使得孕期超声重复辐照的安全性备受关注。有研究显示孕妇的大脑结构与功能非常复杂，孕期接受超声辐照很难对仔鼠自发活动产生影响，但是可导致仔鼠学习记忆能力下降[13-15]。本研究显示辐照过程中无孕鼠死亡，短时间辐照组、长时间辐照组仔鼠第 30 d 与 60 d 的总路程、中央路程、中央时间都短于对照组，长时间辐照组短于短时间辐照组。与李萍[16]等学者的研究类似，但是采用的方法不同，该学者探究不同剂量超声重复辐照孕鼠对仔鼠海马 NMDA 受体 NR1，NR2B 亚单位表达及突触结构的影响，探讨超声辐射对仔鼠学习记忆功能影响的分子机制，结果显示 4 min 组大鼠第 1~4 d 逃避潜伏期短于对照组，20 min 组第 1～4 d 逃避潜伏期长于对照组；4 min 组原站台象限停留时间长于对照组，穿越原站台次数多于对照组；20 min 组原站台象限停留时间短于对照组，穿越原站台次数少于对照组。从机制上分析，开场实验可反映机体神经精神变化与行为变化，主要是观察机体对新环境的适应能力以及由此而产生的情绪变化，能较为客观而准确的对仔鼠的自发活动进行评定[17,18]。孕期重复超声辐射可对仔鼠的学习、记忆能力造成影响，在一定程度上可导致小鼠出现生长发育迟缓[19]。还有研究显示重复超声会导致仔鼠体重增加，也会影响其生长发育成熟情况，特别是仔鼠的脑组织对超声较为敏感，超声的机械作用、热效应、空化作用可导致细胞凋亡、脑组织受损、蛋白质变化等生物效应，从而降低仔鼠的学习、记忆能力[20,21]。

大脑是机体非常复杂的器官，空间学习记忆能力依赖于大脑中多个脑区的协同作用，大脑的一些脑区的损害都会对机体的学习记忆能力产生影响[21]。神经系统发育比较复杂，涉及到神经元细胞的迁移、分化、增殖、凋亡、突触形成等。其中细胞凋亡是细胞的一种生理性死亡形式，也被称为程序性细胞死亡[22]。本研究显示短时间辐照组、长时间辐照组仔鼠第 60 d 的神经元细胞凋亡指数都高于对照组，长时间辐照组高于短时间辐照组，栗建辉[23]等学者探讨不同实时三维超声辐照剂量对晚孕胎鼠大脑神经细胞凋亡的影响，结果能显示辐照 5 min 组凋亡细

胞表达率与对照组和假辐照组间比较差异无统计学意义，辐照10 min组凋亡细胞开始增多，辐照20 min、30 min组凋亡细胞表达率明显增强。表明超声重复辐照能促进神经元细胞凋亡。从机制上分析，中枢神经系统对热和超声等物理因子非常敏感，超声辐射可引起脑细胞凋亡增多，从而对脑功能产生损伤[24]。本研究显示短时间辐照组、长时间辐照组仔鼠第60 d的海马组织乙酰胆碱酯酶含量高于对照组，长时间辐照组高于短时间辐照组。乙酰胆碱酯酶含量与机体的记忆功能呈现负相关性，超声辐照可使得海马组织中乙酰胆碱酯酶含量升高，引起仔鼠学习记忆能力降低，可损害机体的胆碱能神经系统，导致仔鼠学习记忆能力降低[25]。与左红艳[26]的研究类似，探讨微波辐射对海马脑区乙酰胆碱含量及其代谢关键酶表达及活性，结果显示微波辐射后6 h和3 d，大鼠海马ACh含量均见升高，说明微波辐射急性暴露可导致大鼠海马ACh合成与代谢增加。还有学者研究发现超声辐照可引起胎肾肾小球与肾小管细胞核染色质不规则稀疏，从而引起胎肾细胞凋亡[27,28]。

仔鼠的学习记忆功能是一个复杂的过程，海马组织与机体注意功能、空间辨别功能密切相关[29]。有研究显示对孕鼠进行重复超声辐射，可造成海马大面积的损伤，导致海马功能的不可逆改变，使学习记忆能力有所改变[30,31]。本研究显示短时间辐照组、长时间辐照组仔鼠第60 d的海马组织NMDA蛋白相对表达水平低于对照组，长时间辐照组低于短时间辐照组。从机制上分析，NMDA受体在调节神经元发育及参与突触可塑性形成中起着关键作用，研究发现降低神经元NMDA受体表达，增加细胞膜体的内吞，减少细胞外钙离子内流，从而导致细胞毒性损伤[32,33]。超声重复辐照可导致海马神经元可塑性改变，引起神经元膜的去极化与钙离子钙超载，从而使得NMDA蛋白水平降低[34]。本研究的结果为临床提供了一定的指导作用，不过本研究也存在一定的不足，由于胚体发育的复杂性和多样性，其超声辐照对仔鼠发育的影响机制还需要进行深入分析。

总之，超声重复辐照孕鼠能抑制仔鼠海马组织NMDA蛋白表达，促进神经元细胞凋亡与提高乙酰胆碱酯酶含量，从而导致其降低仔鼠的自主记忆活动能力。

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