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## 超短波通过上调SPCA1的表达减轻N2a细胞 氧糖剥夺复氧后的损伤

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**[摘要]** **目的:** 研究发现给予脑缺血再灌注损伤大鼠超短波(ultrashort wave, USW)治疗, 可抑制高尔基体应激的重要参与分子——分泌途径衍生钙离子转运ATP酶1(secretory pathway  $Ca^{2+}$ -ATPase 1, SPCA1)表达的下降, 减少高尔基体等细胞器的破坏和神经元细胞的凋亡, 从而减轻脑缺血再灌注损伤。本研究旨在从细胞水平探讨USW对小鼠N2a细胞氧糖剥夺复氧(oxygen-glucose deprivation/reperfusion, OGD/R)损伤及SPCA1表达的影响。**方法:** 将N2a细胞随机分为对照(Con)组、模型(OGD/R)组、USW组。Con组细胞正常培养, OGD/R组给予OGD/R处理, USW组给予OGD/R后用USW进行处理。在倒置光学相差显微镜下观察细胞形态; 采用细胞计数试剂盒-8(cell counting kit-8, CCK-8)检测细胞活性, 双染法流式细胞术检测细胞凋亡, 蛋白质印迹法检测SPCA1的表达。**结果:** Con组细胞多数呈梭形, 轮廓清晰, 贴壁良好; OGD/R组细胞皱缩, 轮廓模糊, 贴壁性变差, 出现较多悬浮死细胞; 与OGD/R组比较, USW组细胞形态和贴壁性改善, 轮廓更清晰, 死细胞减少。与Con组比较, OGD/R组细胞活性降低, 凋亡率增高, SPCA1表达水平下调, 差异均具有统计学意义(均 $P<0.001$ ); 与OGD/R组比较, USW组细胞活性增加, 凋亡率降低, SPCA1表达水平上调, 差异均具有统计学意义( $P<0.01$ 或 $P<0.001$ )。**结论:** USW可减轻细胞OGD/R后的损伤, 其保护作用可能与上调SPCA1的表达有关。

**[关键词]** 超短波; 氧糖剥夺复氧; 分泌途径衍生钙离子转运ATP酶1; 凋亡; 高尔基体应激

## Ultrashort wave alleviates oxygen-glucose deprivation/ reoxygenation injury via up-regulation of SPCA1 expression in N2a cells

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### ABSTRACT

**Objective:** Application of ultrashort wave (USW) to rats with cerebral ischemia and reperfusion injury could inhibit the decrease of expression of secretory pathway  $Ca^{2+}$ -

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ATPase 1 (SPCA1), an important participant in Golgi stress, reduce the damage of Golgi apparatus and the apoptosis of neuronal cells, thereby alleviating cerebral ischemia-reperfusion injury. This study aims to investigate the effect of USW on oxygen-glucose deprivation/reperfusion (OGD/R) injury and the expression of SPCA1 at the cellular level.

**Methods:** N2a cells were randomly divided into a control (Con) group, an OGD/R group, and an USW group. The cells in the Con group were cultured without exposure to OGD. The cells in the OGD/R group were treated with OGD/R. The cells in the USW group were treated with USW after OGD/R. Cell morphology was observed under the inverted phase-contrast optical microscope, cell activity was detected by cell counting kit-8 (CCK-8), apoptosis was detected by flow cytometry, and SPCA1 expression was detected by Western blotting.

**Results:** Most of the cells in the Con group showed spindle shape with a clear outline and good adhesion. In the OGD/R group, cells were wrinkled, with blurred outline, poor adhesion, and lots of suspended dead cells appeared; compared with the OGD/R group, the cell morphology and adherence were improved, with clearer outlines and fewer dead cells in the USW group. Compared with the Con group, the OGD/R group showed decreased cell activity, increased apoptotic rate, and down-regulating SPCA1 expression with significant differences (all  $P < 0.001$ ); compared with the OGD/R group, the USW group showed increased cell activity, decreased apoptotic rate, and up-regulating SPCA1 expression with significant differences ( $P < 0.01$  or  $P < 0.001$ ).

**Conclusion:** USW alleviates the injury of cellular OGD/R, and its protective effect may be related to its up-regulation of SPCA1 expression.

## KEY WORDS

ultrashort wave; oxygen-glucose deprivation/reperfusion; secretory pathway  $Ca^{2+}$ -ATPase 1; apoptosis; Golgi apparatus stress

缺血性脑卒中已成为威胁全球人类生命健康的主要疾病之一<sup>[1]</sup>, 占有脑卒中类型的 70%~80%, 治疗仍较棘手, 早期溶栓是首选, 但血管再通不可避免地造成再灌注损伤<sup>[2]</sup>, 因此如何减轻和抑制缺血再灌注损伤已成为治疗缺血性脑卒中的关键。目前, 针对缺血再灌注损伤, 药物的治疗作用有限<sup>[3-4]</sup>, 非药物治疗得到越来越多的重视。超短波(ultrashort wave, USW)在临床广泛地被应用于各种神经损伤的治疗, 在脊髓损伤、海马病变、周围神经损伤等疾病的治疗中表现出有效性和潜力<sup>[5]</sup>。研究<sup>[6-9]</sup>发现: 阻断大鼠大脑中动脉后, 给予无热量 USW 治疗, 可以抑制分泌途径衍生钙离子转运 ATP 酶 1(secretory pathway  $Ca^{2+}$ -ATPase 1, SPCA1)表达的下降, 减少高尔基体等细胞器的损伤和神经元细胞的凋亡, 减轻脑水肿, 缩小脑梗死体积, 从而减轻脑缺血再灌注损伤。SPCA1 作为特异性高尔基体膜蛋白, 是高尔基体应激的重要参与分子, 可反映高尔基体应激的水平。研究<sup>[10]</sup>发现: 给予 N2a 细胞氧糖剥夺复氧

(oxygen-glucose deprivation/reperfusion, OGD/R)处理后, SPCA1 表达水平降低, 嗅黏膜间充质干细胞的治疗作用被削弱。在体外实验中, 无热量 USW 对 OGD/R 损伤是否同样具有保护作用, 目前尚未见相关研究。本研究拟通过建立 OGD/R 细胞模型, 探讨 USW 对 N2a 细胞 OGD/R 的保护作用及其机制。

## 1 材料与方法

### 1.1 材料

#### 1.1.1 细胞

N2a 细胞购于长沙维世尔生物科技有限公司, 并在含有 10% 胎牛血清的 Dulbecco's 改良 Eagle 培养基 (Dulbecco's modified Eagle medium, DMEM) 中, 于 37 °C, 5%  $CO_2$  培养箱中培养。

#### 1.1.2 主要试剂和仪器

高糖 DMEM(货号: D5796)购于美国 Sigma 公司; 放射免疫沉淀分析 (radio-immunoprecipitation assay,

RIPA)裂解液(货号: P0013B)、胰蛋白酶(货号: C0201)、青霉素和链霉素双抗(货号: SV30010)购于上海碧云天生物技术有限公司; *D*-Hanks平衡盐溶液购于中南大学湘雅二医院中心实验室; 胎牛血清(货号: 10099141)购于美国Gibco公司; 蛋白磷酸酶抑制剂(货号: P1260)购于北京普利莱基因技术有限公司; BCA蛋白定量试剂盒(货号: AWB0104)购于长沙艾碧维生物科技有限公司; 兔抗SPCA1一抗(货号: 13310-1-AP, 1:750)、辣根过氧化物酶标记的山羊抗小鼠二抗(货号: SA00001-1, 1:5 000)均购于美国Proteintech公司; 发光液(货号: K-12045-D50)购于美国Advansta公司; 细胞计数试剂盒-8(cell counting kit-8, CCK-8)(货号: BW-62)购于日本同仁公司; 凋亡试剂盒(货号: KGA1030)购于江苏凯基生物技术股份公司; 进口手提便携式USW治疗仪(型号: UWM-02)购于日本丸高公司; 倒置光学相差显微镜(型号: DSZ2000X)购于北京中显恒业仪器仪表有限公司; 缺氧培养箱(0% O<sub>2</sub>, 95% N<sub>2</sub>, 5% CO<sub>2</sub>, 37 °C)购于美国MI公司; 流式细胞分析系统(型号: FC 500 MCL/MPL)购于美国Beckman Coulter公司; Bio-Tek酶标仪(型号: MB-530)购于深圳市汇松科技发展有限公司。

## 1.2 OGD/R模型的建立

取处于对数生长期的N2a细胞, 弃培养基, 更换为*D*-Hanks平衡盐溶液, 于缺氧培养箱中培养4 h, 随后将*D*-Hanks平衡盐溶液更换为含有10%胎牛血清和1%青霉素和链霉素双抗的高糖DMEM, 再将N2a细胞于普通细胞培养箱中复氧24 h。

## 1.3 细胞分组及处理

将N2a细胞随机分为3组: Con组, 细胞正常培养, 不进行OGD/R及USW处理。OGD/R组, 给予OGD/R后, 不予USW处理。USW组: 给予OGD/R处理后, 再用USW处理。采用USW治疗仪每天于固定时间进行照射, 对置, 电极距离细胞皿表面约10 cm, 剂量选择按钮置于无热量, 并使用氙灯管检测以确保该输出强度为无热量(判断标准: 可见微弱灯光)。每次治疗10 min, 每天1次, 连续治疗6 d。

## 1.4 观察指标

### 1.4.1 大体形态观察

OGD/R后6 d于倒置相差光学显微镜下观察3组细胞的形态、轮廓、密度、贴壁性、死亡细胞数量等, 评估OGD/R对细胞的影响。

### 1.4.2 CCK-8法检测细胞活性

当N2a细胞生长到对数期时, 用胰蛋白酶消化后

离心收集细胞; 调节细胞密度至 $5 \times 10^4$ /mL, 将细胞接种至96孔板内, 每孔约 $5 \times 10^3$ 个细胞(100  $\mu$ L细胞悬液)。各组均设5个复孔, 培养贴壁后按照前述分组处理后, 避光下缓慢向每孔加入10  $\mu$ L CCK-8试剂。将96孔板置于37 °C, 5% CO<sub>2</sub>下继续孵育4 h后, 用Bio-Tek酶标仪分析450 nm处吸光度值。

### 1.4.3 双染法流式细胞术检测细胞凋亡

用胰蛋白酶消化各组细胞后, 用预冷的PBS轻柔洗涤细胞2次, 以2 000 r/min离心5 min, 收集约 $5 \times 10^5$ 个细胞; 向细胞中加入500  $\mu$ L结合缓冲液, 用移液枪吹打细胞使细胞充分重悬; 在细胞悬浮液中加入5  $\mu$ L Annexin V-APC染色液, 混匀, 再加入5  $\mu$ L PI染色液, 使其充分混匀, 在室温、避光条件下反应5~15 min, 1 h内用流式细胞仪检测。

### 1.4.4 蛋白质印迹法检测SPCA1表达

收集细胞, 提取蛋白质, 用预冷的PBS洗涤细胞, 加入RIPA裂解液后, 在冰上裂解细胞30 min, 离心(12 000 r/min, 15 min)后取上清液, 得到总蛋白质溶液。根据BCA蛋白定量试剂盒说明书测定蛋白质浓度, 加入上样缓冲液, 行SDS聚丙烯酰胺凝胶电泳, 并转移到聚偏二氟乙烯膜上, 将膜在室温下封闭2 h后, 加入稀释的SPCA1一抗在4 °C下孵育过夜。经TBST洗涤后, 加入稀释的二抗, 于室温下孵育1 h, 用缓冲液洗涤3次, 每次3~5 min(摇床上作用)。条带用发光液显影, 将曝光后的条带进行扫描存档, 采用Image J软件分析条带的灰度值。蛋白质的相对表达量为SPCA1与 $\beta$ -actin的灰度值之比。

## 1.5 统计学处理

采用统计软件GraphPad Prism 9分析数据。数据以均数 $\pm$ 标准差( $\bar{x} \pm s$ )表示。组间比较采用单因素方差分析, 之后用Tukey法进行两两比较, 以 $P < 0.05$ 为差异有统计学意义。

## 2 结果

### 2.1 USW对OGD/R处理的N2a细胞形态的影响

Con组N2a细胞大部分呈梭形, 具有神经细胞的轴突样结构, 部分呈圆形、不规则形, 细胞轮廓清晰, 表面光滑, 贴壁良好, 数量最多, 少见悬浮的死细胞。OGD/R组细胞形态轮廓变得模糊, 细胞皱缩, 贴壁性变差, 数量明显减少, 可见较多悬浮的死细胞团。USW组细胞形态改善, 轮廓清晰, 贴壁性变好, 数量较OGD/R组多, 悬浮的死细胞团减少(图1)。

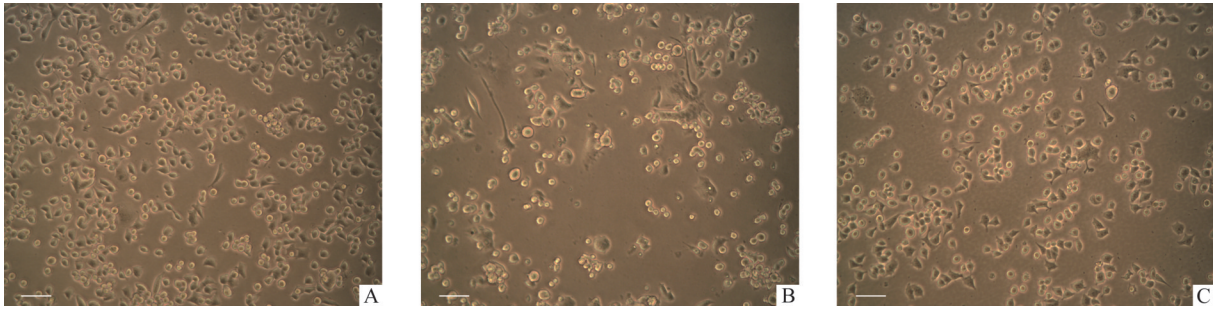


图1 倒置相差光学显微镜下N2a细胞的形态

Figure 1 Morphology of N2a cells under the inverted phase-contrast optical microscope

A: Con group. N2a cells are spindle shaped, with axonal like structures of nerve cells. The cell boundary is clear, the surface is smooth, and the adhesion to the wall is good. The dead cells are rare. B: OGD/R group. The morphology and contour of the N2a cells become blurred and shrunk. The adhesiveness is decreased. The number of living cells is significantly decreased, with more suspended dead cell clusters visible. C: USW group. The morphology of N2a cells gradually recovers, the contour is clear, and the adhesion performance improves. The number of living cells is more than that in the OGD/R group, with less suspended dead cell clusters visible. Con: Control; OGD/R: Oxygen-glucose deprivation/reperfusion; USW: Ultrashort wave. Scale bar=100  $\mu$ m.

2.2 USW对OGD/R处理细胞活性的影响

3组间的细胞活性差异有统计学意义( $F=252.75$ ,  $P<0.001$ )。与Con组相比, OGD/R组细胞活性明显降低( $P<0.001$ ); 与OGD/R组相比, USW组细胞活性明显增加( $P<0.001$ , 图2)。

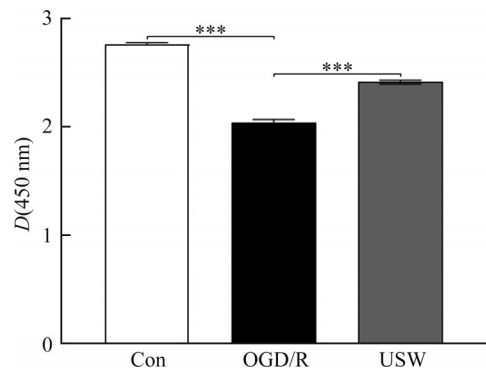


图2 3组细胞活性的比较

Figure 2 Comparison of cell activity among the 3 groups

\*\*\* $P<0.001$ . Con: Control; OGD/R: Oxygen-glucose deprivation/reperfusion; USW: Ultrashort wave.

2.3 USW对OGD/R处理细胞凋亡率的影响

3组间的细胞活性差异有统计学意义( $F=366.8$ ,  $P<0.001$ )。与Con组相比, OGD/R组细胞凋亡率明显增高( $P<0.001$ ); 与OGD/R组相比, USW组细胞凋亡率明显降低( $P<0.001$ , 图3)。

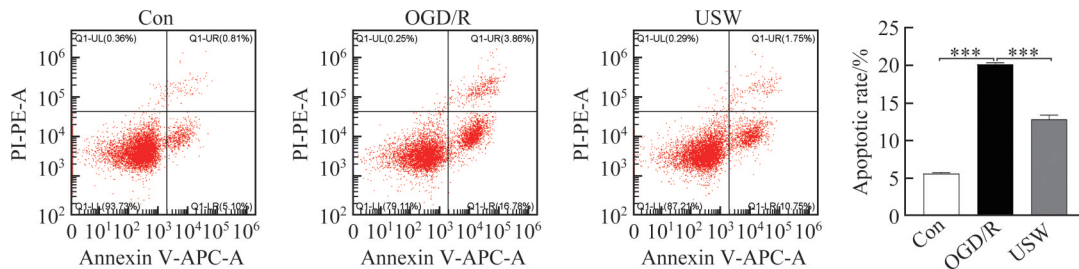


图3 3组细胞凋亡率的比较

Figure 3 Comparison of cell apoptotic rate among the 3 groups

\*\*\* $P<0.001$ . Con: Control; OGD/R: Oxygen-glucose deprivation/reperfusion; USW: Ultrashort wave.

## 2.4 USW对OGD/R处理细胞SPCA1蛋白质表达的影响

与Con组相比, OGD/R组细胞SPCA1蛋白质表

达明显下调( $P<0.001$ ); 与OGD/R组相比, USW组细胞SPCA1蛋白质表达明显上调( $P<0.01$ , 图4)。

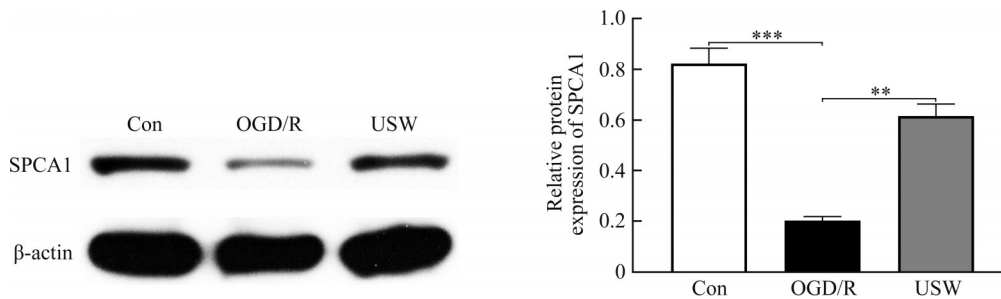


图4 3组细胞SPCA1蛋白质表达水平的比较

Figure 4 Comparison of level of SPCA1 protein expression among the 3 groups

\*\* $P<0.01$ , \*\*\* $P<0.001$ . Con: Control; OGD/R: Oxygen-glucose deprivation/reperfusion; USW: Ultrashort wave; SPCA1: Secretory pathway  $Ca^{2+}$ -ATPase 1.

## 3 讨论

无热量USW是一种无创的高频电疗, 作为常见的物理因子疗法, 在临床上已成为多种疾病的辅助治疗手段<sup>[11-12]</sup>。动物试验<sup>[13]</sup>已证实USW可减轻大鼠脑水肿, 缩小脑梗死体积, 促进神经功能恢复, 减轻脑缺血再灌注损伤。在本研究中, 对N2a细胞进行OGD/R处理后, 细胞皱缩减少, 细胞活力明显下降, 凋亡率明显增高, 与既往的研究<sup>[14]</sup>结果一致, 表明成功地建立了OGD/R的细胞模型。进一步给予OGD/R模型细胞USW处理6d后, 细胞形态改善, 细胞活性增加, 凋亡率下降。因此, 笔者认为无热量USW可以通过抑制凋亡来减轻细胞OGD/R损伤。

在脑缺血再灌注过程中, 活性氧过多导致氧化应激, 氧化应激在缺血再灌注损伤的发生和发展过程中起重要作用<sup>[15]</sup>。高尔基体作为氧化应激的功能和效应细胞器, 高尔基体应激<sup>[16]</sup>是高尔基体对氧化应激所作的应答, 高尔基体膜离子泵活性的改变是其主要表现形式之一。SPCA1作为特异性定位于高尔基体的跨膜蛋白, 在细胞质和高尔基体之间 $Ca^{2+}$ 的转运中起重要作用, 对调节高尔基体内 $Ca^{2+}$ 水平有重要意义<sup>[17-18]</sup>。SPCA1的表达水平可以反映高尔基体应激的程度。当发生脑缺血再灌注损伤时, SPCA1的活性和表达下降, 其摄取细胞质内 $Ca^{2+}$ 的能力也受损, 加剧了细胞质内 $Ca^{2+}$ 超载, 而 $Ca^{2+}$ 超载是脑缺血再灌注损伤发生的分子机制之一。细胞内 $Ca^{2+}$ 水平持续过高通常会导致神经细胞过度皱缩, 蛋白质水解, 高尔

基体碎裂, 并最终导致细胞死亡。同时,  $Ca^{2+}$ 超载也会增强氧化应激, 上述因素相互作用, 共同促进缺血再灌注损伤的病理过程。本研究发现: 给予N2a细胞OGD/R处理后, SPCA1表达水平下调, 细胞凋亡增加, 其机制可能与SPCA1表达下降后细胞质内 $Ca^{2+}$ 水平上升, 钙超载加剧有关。

以往关于USW在亚细胞器水平对缺血性脑卒中的神经保护作用的机制研究较少。本课题组前期的研究<sup>[13, 19-20]</sup>发现: USW可上调脑缺血再灌注损伤大鼠SPCA1的表达, 减轻高尔基体应激, 从而发挥神经保护作用。通过短发夹RNA抑制SPCA1的表达会加重缺血再灌注损伤<sup>[20]</sup>。这些研究均证明USW对脑缺血再灌注损伤的神经保护作用与其上调SPCA1表达, 减轻高尔基体应激有关。本研究则首次在细胞水平证实USW上调经OGD/R处理后N2a细胞中SPCA1的表达, 减少细胞凋亡, 发挥保护神经细胞的作用。

综上, 本研究成功利用N2a细胞建立OGD/R细胞模型, 并发现USW处理可减少OGD/R后的细胞凋亡, 抑制细胞活性下降, 减轻OGD/R损伤, 发挥保护神经细胞作用, 其机制可能与上调SPCA1表达及调控高尔基体应激水平有关。

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