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Protection of androgen against hypoxic-ischemic brain damage in neonatal rats and possible mechanisms

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Abstract: **Objective** Some research has shown that androgen has a neuroprotection against hypoxia-ischemia brain damage (HIBD). However, the relevant mechanism has not been fully elucidated. This study aimed to explore the neuroprotection of androgen against HIBD in neonatal rats and the possible mechanism. **Methods** Sixty-four seven-day-old Sprague-Dawley (SD) rats were randomly assigned into three groups: Sham-operation, HIBD and Androgen. The HIBD model was induced by ligation of the left carotid common artery along with hypoxia exposure in neonatal rats from the latter two groups. The Sham-operation group was not subjected to hypoxia-ischemia (HI). The Androgen intervention group received an injection of testosterone propionate (25 mg/kg) immediately after HIBD. Bcl-2 and Bax protein expressions in the cortex and hippocampal CA region were detected by immunohistochemical method at 6, 24 and 72 hrs and at 7 days after HI. The contents of SOD and MDA in the brain tissue homogenate were measured by the thiobarbituric acid (TBA) method and the xanthine oxidase luminescence method respectively at 6, 24 and 48 hrs after HI. **Results** There were few Bcl-2 and Bax immune positive cells in the cortex or hippocampus in the left hemisphere in the Sham-operation group at 6 hrs after operation. This was significantly different from the HIBD control and Androgen intervention groups ($P < 0.01$). The expression of Bcl-2 protein in the cortex and hippocampus of the Androgen intervention group was significantly higher than that of the HIBD control group at 6, 24 and 72 hrs after HI ($P < 0.05$ or 0.01). The expression of Bax protein in the cortex and hippocampus of the Androgen intervention group was significantly lower than that of the HIBD control group at 24 hrs after HI ($P < 0.05$). The SOD content in the brain tissue homogenate of the HIBD control group was significantly reduced, in contrast, the MDA content in the brain tissue homogenate of the HIBD control group increased significantly at 6 hrs after HI compared with the Sham-operation group ($P < 0.05$). The SOD content was reduced to a nadir and the MDA content increased to a peak at 24 hrs after HI in the HIBD control group. Androgen intervention increased significantly the SOD activity at 6, 24 and 48 hrs after HI and decreased significantly the MDA content at 6 and 24 hrs after HI as compared with the HIBD control group ($P < 0.05$ or 0.01). **Conclusions** The neuroprotection of androgen against neonatal HIBD is produced possibly through an increase of Bcl-2 protein expression and a reduction in Bax protein expression, thus decreasing neuronal apoptosis after HI. There may also be a reduction in the consumption of antioxidant and an inhibition of the formation of oxidant free radicals to alleviate neuronal damage following HI.

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Key words: Hypoxic-ischemic brain damage; Androgen; Bax; Bcl-2; SOD; MDA; Neonatal rats

雄激素对新生大鼠缺氧缺血脑损伤的保护作用及机制研究

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[**摘　要**] **目的**　雄激素对缺氧缺血后脑损伤有神经保护作用,但其作用机制尚不完全清楚。该研究探讨雄激素对缺氧缺血性脑损伤(HIBD)的保护作用及其可能的机制。**方法**　64 只 7 日龄 SD 大鼠随机分为假手术组、HIBD 对照组和雄激素干预组。通过结扎左颈总动脉和吸入 8% 氧气和 92% 氮气的混合气体制备新生鼠 HIBD 模型。假手术组仅做颈正中切口,游离左颈总动脉,不结扎, 不行低氧处理。雄激素干预组在模型制成后即刻注射丙酸睾丸酮(25 mg/kg)。缺氧缺血(HI)后 6 h、24 h、72 h、7 d 取脑组织制作石蜡切片,用免疫组化法观察 Bcl-2 和 Bax 蛋白在各组大鼠皮质和海马表达的动态变化。HI 后 6 h、24 h、48 h 断头取脑制作脑匀浆,测定 SOD 活性和

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MDA 含量。**结果** 假手术组大鼠左脑的皮质及海马可见少量 Bcl-2 蛋白和 Bax 蛋白免疫阳性细胞表达,与 HIBD 对照组和雄激素干预组比较差异均有显著性意义($P < 0.01$)。雄激素干预组 HI 后 6 h、24 h、72 h Bcl-2 蛋白在皮层和海马的表达水平明显高于 HIBD 对照组($P < 0.05$ 或 0.01)。雄激素干预组 Bax 蛋白的表达水平在 HI 后 24 h 显著低于 HIBD 对照组($P < 0.05$),其他时间点两组 Bax 蛋白的表达无明显差别。与假手术组比较,HIBD 对照组 HI 后 6 h 大鼠脑组织中 SOD 活性明显降低, MDA 含量明显增加($P < 0.05$)。HIBD 对照组 HI 后 24 h SOD 活性降至最低值, MDA 含量升至最高。雄激素干预增加了 SOD 活性, 雄激素干预组 HI 后 6 h、24 h、48 h SOD 活性均明显高于 HIBD 对照组, 差异有显著性意义($P < 0.05$ 或 0.01)。雄激素干预亦导致了脑组织中 MDA 含量降低, 雄激素干预组 HI 后 6 h、24 h MDA 含量均明显低于 HIBD 对照组,差异有显著性意义(分别 $P < 0.05$、$P < 0.01$)。**结论** 雄激素发挥脑保护作用可能通过上调 Bcl-2 蛋白、下调 Bax 蛋白表达以及通过减少抗氧化剂的消耗和抑制氧自由基的生成, 从而减轻缺氧缺血后神经细胞的损伤。 [中国当代儿科杂志,2006,8(6):441 - 446]

[关 键 词] 缺氧缺血性脑损伤; Bcl-2; Bax; SOD; MDA; 新生大鼠
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The pathogenesis of neonatal hypoxic-ischemic brain damage (HIBD) is rather complicated, involving many factors like metabolic disturbance of cellular energy, oxidative damage of free radicals, cell apoptosis and toxicity of excitatory amino acid. If these factors are blocked at an early stage, the severity of HIBD will be alleviated apparently and the prognosis will also be improved. Studies have shown that androgen has neuroprotective effects against HIBD[1,2]. However, the relevant mechanisms has not been fully identified. It is a new research project to investigate the protection of androgen on HIBD and relevant mechanisms. A HIBD model of the neonatal rat was prepared in this study. The protection of androgen on HIBD and its possible mechanisms were studied by examining the changes of B-cell lymphoma/leukemia-2 (Bcl-2), Bcl-associated x protein (Bax), malondialdehyde (MDA) and superoxide dismutase (SOD) in the brain tissue of HIBD rats after androgen administration and comparing these changes with the controls.

Materials and methods

Materials

Sixty-four seven-day-old first-class Sprague-Dawley (SD) rats of both sexes, weighing 12-18 g, were provided by the Center of Experimental Animals at the Fourth Military Medical University. Testosterone propionate injection (25 mg in 1 mL), batch number 0303232, was provided by Tianjin Jinyao Amino Acids Co. Ltd.. The reagent kits for SOD and MDA were provided by Nanjing Jiancheng Biological Products Co. Ltd.. Bcl-2 rabbit anti-rat antibody, SABC reagent kit and DAB chromogenic reagent kit were provided by Wuhan Boshide Bioengineering Co. Ltd..

Methods

Establishment of HIBD model of neonatal rats

The seven-day-old SD rats were anesthetized with ether. They were then placed on their backs and their limbs were fixed to the operation board. The rats were cut right in the middle of the neck and the left common carotid artery was freed. Then the cut was ligated and sealed with 6-0 surgical silk. After 2-3 hours recovery, the rats were placed in the self-made hypoxic room. Mixed air with 8% oxygen and 92% nitrogen was introduced into the room at a speed of 1-2 L/min and the concentration of oxygen was monitored by an oxygen detector. The rats were taken out after about 2.5 hours.

The rats which were only cut right in the middle of the neck and only had their left common carotid artery freed but not ligated, had a sham operation.

Grouping of the animals

The 64 neonatal rats were randomly assigned into a Sham-operation group, a HIBD group and an Androgen group. The rats in the Androgen group were given an intraperitoneal injection of 25 mg/kg testosterone propionate immediately after HI.

Preparation of brain tissue slice and immunohistochemical staining

At each time interval of 6, 24 and 72 hrs and at 7 days after HI, four rats of the HIBD and Androgen groups were randomly chosen and were sacrificed for the preparation of brain tissue samples. In the Sham-operation group samples of four rats were only taken at 6 hours. Each rat was anaesthetized and the chest was cut to expose the heart. A tube was intubated from the left ventricle to the aorta and the heart was perfused and fixed with 4% paraformal-dehyde in 0.55 mol/L phosphate buffer. In reference to the "Rat Brain Stereotaxic Atlas", the skull was cut with a coronal cut from the mammillary body at the level of optic chiasma

in order to take out the brain. The brain was fixed in the 4% paraformal-dehyde for a night and was embedded in paraffin. The slice was 5 μm thick.

The SABC method was used for immunohistochemical stainings of Bcl-2 and Bax. A control experiment was conducted, i.e, rabbit anti-rat Bcl-2 solution was replaced with 0.01 MPBS solution and the other procedures were the same; the slice was sealed with neutral gum; the brain tissue sample without rabbit anti-rat I antibody addition was defined as negative blank control (with PBS as a substitution) and the cells that had yellow particle sediment in the cytoplasm and nucleus were positive cells.

The semi-quantitative method was used for the counting of immunohistochemical positive cells. Under the 40 × field lens, 6 fields of nonoverlapping cerebral cortex or hippocampuses in each slice of the left brain were chosen and the Bcl-2 and Bax immunohistochemical positive cells were counted. The cells which the color of the stained cytoplasm was claybank or tan were defined as immunohistochemical positive. The average of the number of positive cells of all the rats in each group ± standard deviation ($\bar{x} \pm SD$) was taken as the number of the immunohistochemical positive cells of Bcl-2 and Bax in the cerebral cortex or hippocampus.

Preparation of brain tissue homogenate and the determination of SOD and MDA

At each time interval of 6, 24 and 48 hours after HI, four rats of the HIBD and Androgen groups were randomly chosen and were sacrificed for the preparation of brain tissue homogenate. In the Sham-operation group samples of four rats were only taken at 6 hours. After the rats were sacrificed, the brains were removed. The two hemispheres were separated in the ice floe. The left hemisphere was rinsed in the 4 ℃ normal saline to remove the blood. After it was dried, 200 mg of brain tissue was taken. 4 ℃ normal saline was used as the homogenate medium. The proportion of the brain to the saline was 1 g : 9 mL. The brain homogenate was made with a tissue grinder in a vessel filled with ice . The homogenate was centrifugated for 20 minutes at a speed of 3 000 r/min. The supernatant clear solution was then stored in a − 4 ℃ refrigerator for the measurement of MDA and SOD. The MDA content was determined with the thiobarbituric acid (TBA) method . The SOD content was determined by the xanthine oxidase luminescence method.

Statistical analysis

The measured data were inputted into Excel 7.0 software and analyzed with SPSS10.0 software. Data were shown as $\bar{x} \pm s$ for ANOVA analysis . The average of two samples was tested with t testing. $P < 0.05$ was believed to be statistically significant.

Results

The expression of Bcl-2 protein in the brain tissue

In the Sham-operation group, there were few Bcl-2 immune positive cells which were yellow under the microscope in the cortex or hippocampus of the left hemisphere. The expression of Bcl-2 immune positive cells in the cortex or hippocampus in the left hemisphere of the rats began to increase at 6 hrs after HI, reached a peak at 72 hrs after HI and then began to fall. A relatively low level was maintained at 7 days after HI. Bcl-2 protein was present as particle or streak in the cytoplasm and had the same distribution place as the cellular organs. The nucleus membrane was sometimes stained. The changed course of Bcl-2 expression in the cortex or hippocampus of the left hemisphere in the Androgen group was similar to the HIBD group. However, the number of Bcl-2 immune positive cells in the Androgen group was significantly greater than that in the HIBD group at 6, 24 and 72 hrs after HI ($P < 0.05$ or 0.01). See Table 1 and Figure 1.

The expression of Bax protein in the brain tissue

In the Sham-operation group, there were very few Bax protein immune positive cells in the cortex or hippocampus in the left hemisphere of the rats. The expression of Bax protein immune positive cells in the cortex or hippocampus in the left hemisphere of the rats began to increase 6 hours after HI, and reached a peak at 24 hours after HI. Then the Bax protein expression began to decrease and was maintained at a relatively

Table 1 The Bcl-2 and Bax expressions after HI ($\bar{x} \pm s$)

Group	6 hrs		24 hrs		72 hrs		7 days	
	Bcl-2	Bax	Bcl-2	Bax	Bcl-2	Bax	Bcl-2	Bax
Sham-operation	11.67 ± 1.76	4.83 ± 1.47	—	—	—	—	—	—
HIBD	22.17 ± 3.43[a]	15.50 ± 4.51[a]	53.67 ± 4.63	60.52 ± 4.64	66.00 ± 2.97	22.17 ± 2.32	16.33 ± 2.81	17.50 ± 5.17
Androgen	26.67 ± 4.41[a,b]	15.67 ± 3.98[a]	59.17 ± 4.45[b]	54.68 ± 4.76[b]	71.33 ± 4.08[c]	21.33 ± 2.80	17.34 ± 2.42	17.33 ± 4.32

a $P < 0.01$ (compared to the Sham-operation group); b $P < 0.05$, c $P < 0.01$ (compared to the HIBD group)

Table 2 The contents of SOD (U/mg prot) and MDA(nmoL/mg prot) after HI ($\bar{x} \pm s$)

Group	6 hrs		24 hrs		48 hrs	
	SOD	MDA	SOD	MDA	SOD	MDA
Sham-operation	60.67 ± 7.26	2.45 ± 0.87	—	—	—	—
HIBD	51.39 ± 7.17[a]	3.27 ± 0.58[a]	46.41 ± 3.74	3.66 ± 0.83	56.53 ± 10.90	3.05 ± 0.92
Androgen	61.76 ± 10.54[b]	2.63 ± 0.52[b]	56.68 ± 3.53[c]	2.73 ± 0.90[c]	64.81 ± 3.63[b]	2.36 ± 0.76

a $P < 0.05$ (compared to the Sham-operation group); b $P < 0.05$, c $P < 0.01$ (compared to the HIBD group)

low level at 7 days after HI. The changed course of Bax protein expression in the cortex or hippocampus of the left hemisphere in the Androgen intervention group was similar to the HIBD group. However the expression number of Bax protein immune positive cells at 24 hours after HI in the Androgen group was significantly less than that in the HIBD control group ($P < 0.05$). See Table 1 and Figure 2.

SOD activity in the homogenate of brain tissue

The SOD activity in the homogenate of brain tissue in the Sham-operation group was 60.67 ± 7.26 U/mg prot, which was noticeably higher than that in the HIBD group at 6 hours after HI. The SOD activity was reduced to a nadir at 24 hours after HI in the HIBD group. Androgen intervention increased significantly the SOD activity at 6, 24 and 48 hours after HI when compared with the HIBD group. See Table 2.

MDA content in the brain tissue

The MDA content in the brain tissue in the Sham-operation group was 2.45 ± 0.87 nmol/mg prot. It began to increase significantly at 6 hours after HI and reached a peak at 24 hours after HI in the HIBD group. Androgen decreased noticeably the MDA content at 6 and 24 hours after HI as compared with the HIBD group. The MDA content of the Androgen group at 48 hrs after HI was also lower than that of the HIBD group, but the differences were not significant. See Table 2.

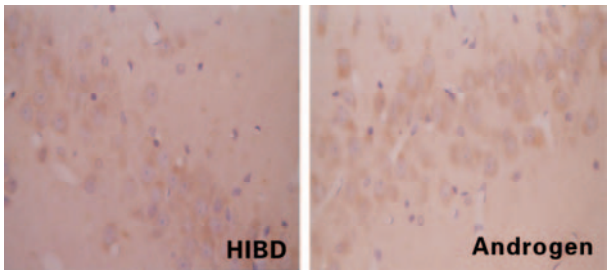

Figure 1 Bcl-2 expression in the hippocampus (×40). The number of Bcl-2 immune positive cells in the Androgen group was significantly greater than that in the HIBD group at 24 hrs after HI.

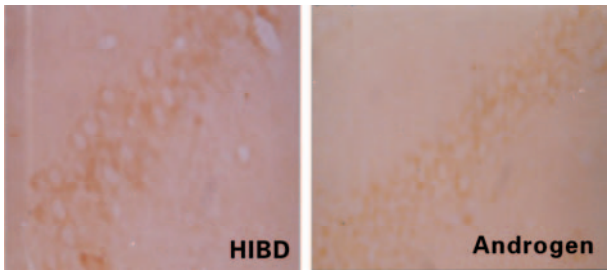

Figure 2 Bax expression in the hippocampus (×40). The number of Bax immune positive cells in the Androgen group was significantly less than that in the HIBD group at 24 hrs after HI.

Discussion

By using the kainic acid-induced convulsion rat model, Ramsden[1] discovered that the number of apoptotic neurons in the hippocampus CA area in the brain of the normal male rat was the least while that in the emasculated male rats apparently increased. A supplement of exogenetic androgen DHT significantly reduced the number of apoptotic neurons. This suggested that endogenous androgen played an important role in maintaining the survival of neuron and that a supplement of exogenetic androgen can also protect the damaged neurons similarly. Li[2] prepared a whole cerebral ischemia model with the Wistar male rat. The neuropathological detection discovered that the death rate of neuron in the CA area decreased from (88 ± 13)% in the placebo group to (60 ± 7)% in the DHEA group. The difference was significant. This showed that DHEA can reduce neuronal apoptosis after transient cerebral ischemia. Garcia-Segura[3] found that androgen can reduce hyperplasia of spongiocyte in the damaged area, inhibit the formation of glial scar and promote the growth of neuraxon in the damaged area. Bimonte-Nelson[4] also

found that exogenetic testosterone can apparently improve the memory of old rats and can lead to an obvious expression of nerve growth factor in the hippocampus area.

This study observed the changes of two important controlling genes, that is, Bcl-2 which inhibits neuronal apotosis and Bax which promotes neuronal apoptosis, in neonatal rats with HIBD after androgen administration. The results showed that the changed course of Bcl-2 and Bax expressions in the Androgen intervention group was similar to that of the HIBD group. However, the expression of Bcl-2 protein in the cortex or hippocampus in the Androgen group was significantly higher than that of the HIBD group at 6, 24 and 72 hrs after HI. The expression of Bax protein in the Androgen group was a little lower than that of the HIBD group and a significant difference was noted at 24 hours after HI. This suggested that androgen intervention can apparently promote Bcl-2 expression and thus inhibit neuronal apoptosis and that the changes of Bax expression resulting from androgen treatment were not obvious as Bcl-2 expression. This study showed that androgen intervention increased Bcl-2 expression and decreased Bax expression in the cortex or hippocampus, thus providing a neuroprotection against neonatal HIBD.

Some research has proved that oxygen free radicals and lipid peroxidation products play a part in the neuronal damage after HI[5,6]. In the condition of HI, the production of free radicals is too much and surpasses the elimination ability of the body which then leads to the tissue damage. SOD plays an important role in balancing the oxidation of the body. This enzyme can eliminate superoxide anion free radicals and protect the cells from being damaged. It is the main scavenger enzyme of free radicals in the body. The determination of this enzyme can show the endogenous antioxidant ability. MDA is the final product of lipid peroxidation reaction. The determination of MDA can show the lipid peroxidation of free radicals in the brain tissue. In recent years, the relationship between androgen as well as androgen recepator (AR) and HIBD has attracted more and more attention.

The research has shown[7] that androgen is not only related to the maintenance of masculinity, but that it also influences the ability of learning and memory and protects the brain from damage and promotes restoration of brain damage, possibly through AR mediating. AR exists extensively in the nervous system, including hypothalamus, hippocampus, pituitary, cerebellum and cerebral cortex. Ahlbom[8] reported that testosterone had anti-oxidative effects on granular cells of the rat cerebellum possibly through AR mediating.

The results of this research showed that the SOD activity decreased and the MDA content increased in the homogenate of brain tissue after HIBD and that the changes were most obvious 24 hrs after HI. It indicated that the changes of radicals were nearly consistent with the pathophysiologic changes of brain tissue after HI and with the conclusions in the reported literature[9]. Androgen treatment significantly increased the SOD activity and significantly decreased the MDA content in HIBD rat brain homogenateas compared with the HIBD group. This suggests androgen has anti-free radical effects and neuroprotections against the ischemic brain damage. As AR exists widely in the brain, androgen can play the antioxidant role by direct mediating with AR. Besides this, many aromatization enzymes exist in the brain which can transform the androgen into estrogen. Therefore, androgen can also reduce the production of antioxidant through this means[10].

In conclusion, the neuroprotection of androgen against neonatal HIBD is produced possibly through an increase of Bcl-2 protein expression and a reduction in Bax protein expression, thus decreasing neuronal apoptosis after HI. It could also be possibly through a reduction in the consumption of antioxidant and an inhibition of the formation of oxidant free radicals to alleviate neuronal damage following HI.

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·消息·

欢迎订阅《中国当代儿科杂志》

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本刊内容以儿科临床与基础研究并重,反映我国当代儿科领域的最新进展与最新动态。辟有英文论著、中文论著(临床研究、实验研究、儿童保健、疑难病研究)、临床经验、病例讨论、病例报告、专家讲座、综述等栏目。读者对象主要为从事儿科及相关学科的临床、教学和科研工作者。

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