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• 計畫中文名稱	糖皮質激素神經保護作用之基因體研究計畫---脊髓損傷基因機轉研究之動物模式核心設施(III)		
• 計畫英文名稱	--		
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• 中文關鍵字	脊髓損傷; 甲基去氫氧化可體松; 細胞因子信號傳遞抑制體 3(SOCS-3)		
• 英文關鍵字	Spinal cord injury (SCI); Methylprednisolone (MP); Erythropoietin (EPO) Suppressor of cytokine signaling-3 (SOCS-3)		
• 中文摘要	<p>紅血球生成素嚴重的脊髓損傷常常導致下肢癱瘓或四肢癱瘓。到目前為止，甲基去氫氧化可體松(methylprednisolone)仍是美國食品暨藥品管制局所唯一核准用來治療急性脊髓損傷的藥物。然而，對於甲基去氫氧化可體松是如何保護受傷脊髓的作用機轉科學家卻仍不清楚。本整合型計畫的最終目標便是要了解甲基去氫氧化可體松保護脊髓損傷的細胞及分子機制。本動物核心設施的目標便是有效率地提供整合型計畫中的其他子計畫脊髓損傷的動物，以及探討甲基去氫氧化可體松保護脊髓損傷的細胞及分子機制。在第三年的計畫中，本動物核心設施共提供子計畫一、二及四大約二百九十隻的脊髓損傷大鼠，及五十隻左右的脊髓損傷小鼠進行研究。最新的證據顯示去除細胞因子信號傳遞抑制體 3(SOCS-3)的基因顯著改善脊髓損傷小鼠的後肢行動能力。因此，在本計畫中我們要測試兩個假說：一為脊髓損傷是否會影響 SOCS-3 蛋白質的展現，另一為甲基去氫氧化可體松或紅血球生成素是否會影響 SOCS-3 蛋白質的展現。在實驗一，我們將成年的 Long Evans 母鼠隨機分為三組：Sham + Vehicle 組, SCI + Vehicle 組及 SCI + MP 組。在實驗一，我們將 NYU Impactor 十克重的撞擊桿提高到 25mm 的位置，然後將其釋放來造成老鼠的脊髓損傷。在實驗二，我們將成年的 Sprague-Dawley 母鼠隨機分為三組：Sham + Vehicle 組, SCI + Vehicle 組及 SCI + EPO 組。在實驗二，我們使用 IH Impactor 以 200,000 達因的力道來造成老鼠的脊髓損傷。在給予脊髓損傷老鼠控制溶劑 (Sham + Vehicle 組及 SCI + Vehicle 組)、甲基去氫氧化可體松 (30 mg/kg, SCI + MP 組) 或紅血球生成素 (5000I.U./kg, SCI + EPO 組) 四小時之後，我們將一半的動物麻醉後犧牲，並取出大約 5 mm 的未受傷脊髓或損傷脊髓作為萃取蛋白質之用。我們將另外一半的老鼠以生理食鹽水及固定液灌流後，將其脊髓切片後進行 SOCS-3 蛋白質的組織染色。我們的研究結果顯示脊髓損傷會顯著增加 SOCS-3 蛋白質的展現。再者，甲基去氫氧化可體松或紅血球</p>		

生成素會抑制脊髓損傷所引起的 SOCS-3 蛋白質的表現量。甲基去氫氧化可體松或紅血球生成素都被證實會改善脊髓損傷的程度。最新的證據又顯示，剔除 SOCS-3 的基因會改善脊髓損傷小鼠的後肢行動力。本實驗的研究結果及已發表的研究證據強烈建議甲基去氫氧化可體松或紅血球生成素可能經由抑制 SOCS-3 蛋白質的表現而達到其保護受傷脊髓的作用。

Severe spinal cord injury (SCI) often causes paraplegia or tetraplegia. Methylprednisolone (MP) is still the only FDA-approved therapeutic agent for treating patients suffering from acute SCI. Nonetheless, the neuroprotective effects of MP on SCI still remain poorly understood. The ultimate goal of our PPG is to resolve the cellular and molecular mechanisms that mediate the neuroprotective effects of MP on SCI. This animal core aims to support the Component Projects 1, 2 and 4 with SCI animals and to study cellular and molecular mechanisms of glucocorticoid neuroprotection. In the third year, we have provided Component Projects 1, 2 and 4 with approximately 290 SCI rats and 50 SCI mice. Recent evidence demonstrates that deletion of suppressor of cytokine signaling-3 (SOCS-3) gene promotes motor recovery of SCI mice. In this study, we therefore tested the hypotheses that SCI affects the expression of SOCS-3 protein and that MP or erythropoietin (EPO) influences the expression of SOCS-3 protein using the western blotting and immunohistochemical techniques. In Experiment 1, adult female Long Evans rats were randomly distributed into the Sham + Vehicle group, SCI + Vehicle group and SCI + MP group (MP, 30 mg/kg). In Experiment 2, adult female Sprague-Dawley rats were randomly assigned into the Sham + Vehicle group, SCI + Vehicle group and SCI + EPO group (EPO, 5000 I.U./kg). Four hours following vehicle, MP (30 mg/kg) or EPO (5000 I.U./kg) treatment, animals were sacrificed. For half of the animals, sham-lesion or lesion spinal cords were collected and processed for SOCS-3 western blotting. For the other half of the animals, spinal cords were processed for SOCS-3-like immunoreactivity. Our results showed that SCI significantly enhanced the expression of SOCS-3 protein and SOCS-3-like immunoreactivity. Moreover, MP treatment suppressed the SCI-induced expression of SOCS-3 protein and SOCS-3-like immunoreactivity. Similarly, EPO treatment attenuated the SCI-induced expression of SOCS-3 protein and SOCS-3-like immunoreactivity. Because both MP and EPO exert beneficial effects on SCI and SOCS-3 has a detrimental effect on SCI, our current results strongly suggest that MP or EPO may exert its neuroprotective effect on SCI via novel mechanisms by suppression of SOCS-3 expression.

- 英文摘要