# 長期給予懷孕母鼠嗎啡對其所生幼鼠學習與記憶之影響及其分子機制

# The effect of prenatal exposure to morphine on learning and memory and activation of CREB & PKC in the hippocampus of developing rats


## 中文摘要

過去臨床研究發現，懷孕期間施打嗎啡或海洛英成癮的母親所生下的小孩，他們的學習能力以及社會適應比一般正常的孩子來的差，其神經病裡機轉仍未清楚。之前我們實驗室已經證實，在懷孕期間注射嗎啡的母鼠，所生之幼鼠的發育過程中，其海馬迴裡的 N-methyl-D-asparate (NMDA) receptor 以及經由 kainic acid 所誘發之 calcium /calmodulin kinase II（CaMKII）的活性，會顯著比對照組之幼鼠低。如果 NMDA receptor 和 CaMKII 的活化，對學習與記憶的能力很重要，那麼懷孕期接觸嗎啡所生幼鼠其學習與記憶能力的發展有可能受影響。因此為了證實上述的論點，我們以水迷宮的實驗，來偵測懷孕期間注射嗎啡的母鼠，所生之幼鼠其學習與記憶的能力。並且以西方墨點法來測量海馬迴中，兩個與學習記憶相關的蛋白質活化型態即活化型 PKC 和 CREB 的表現量。水迷宮的實驗結果顯示在出生後第 30 天，嗎啡組和控制組幼鼠在學習與記憶的能力上沒有什麼差異。但在出生後第 60 天，嗎啡組的能力都比控制組差。而西方墨點法的結果顯示在出生後第 60 天，嗎啡組的內生性活化型 CREB 明顯的比控制組低。另一方面，出生後第 30 天和第 60 天，嗎啡組和控制組在活化型 PKC 的表現上沒有差異。此外，在所有的實驗老鼠中，嗎啡組和控制組在經由 KA 所誘導活化的 CREB 和 PKC 的表現量，皆無顯著差異，。本篇研究推測發育中的幼鼠在出生以前即受到嗎啡的影響，會降低其學習與記憶的能力。並推測這個結果是由於海馬迴中 NMDA receptor-CaMKII-CREB 此一路徑的活化所受到抑制而造成。

## 英文摘要

Certain neuropsychological sequels, particularly in the ability of learning and social adaptation, have found in children born to mothers addicted to morphine or heroin during pregnancy. The underlying neuropsychological mechanisms we unclear. We, previous had found that rats born to dams rats chronically received daily morphine injection through the whole course of pregnancy had decrease in the expression of N-methyl-D-asparate (NMDA) receptor and kainic acid-induced calcium /calmodulin kinase II activity in the hippocampus during developing stage. Given that activation of the NMDA receptor and CaMKII are essentially required for the function of

learning and memory, it is possible that that prenatal exposure to morphine will cause disability in the learning and memory in the developing rats born to morphine-treated rats. To address this issue we determine the ability of learning and memory in the rats born to dam rats chronically received morphine during prenatal period by water maze experiment. We also determined the expression of two elements downstream to the activation of NMDA receptor and CaMKII, namely, the activation of protein kinase C and cAMP response element binding protein (CREB), in the hippocampus using immunoblotting assay. The study of water maze showed that no change in the ability of learning or memory in the morphine group rats at postnatal day 30 as compared to that of control group rats. However, there is a trend of decrease in both learning and memory ability of morphine group rats on postnatal day (PND) 60. Immunoblotting assay study showed that on PND 30 and 60, the endogenous activated form of CREB of morphine was significantly lower than that of control group rats. On the other hand, no difference in the expression of activated form of PKC between control and morphine group rats on either PND 30 or PND 60. There is no difference between control and morphine group in term of kainic acid-induced activation of CREB and PKC on any examined PND. This study suggests that prenatal exposure to morphine might disturb the development of learning and memory function in the developing rats, and one possible mechanism is through the inhibition in the activation of NMDA receptor-CaMKII-CREB pathway in the hippocampus.