Part I: 長期給予母鼠嗎啡對其所生幼鼠腦部海馬迴中 PSD-95 和 synaptophysin 表現的影響 Part II:探討 serotonin 再吸收抑制劑對於嗎啡幼鼠脫癮症狀的治療效果

Part I: The effect of prenatal exposure to morphine on the expression of PSD-95 and synaptophysin in the hippocampus of developing rats. Part II: The therapeutic effect of serotonin reuptake inhibitor on the expression of morphine withdraw syndrome in ne

中文摘要

Part I -- 中文摘要

我們實驗室先前的研究結果顯示,長期給予懷孕母鼠施打嗎啡其子代 (嗎啡組老鼠) 腦部的海馬迴中發現，在出生後第 14 天的 NMDA (N-methyl-D-aspatate) 接受器有顯著的減少；但在其他天數無此現象。於是我們更進一步的藉由西方墨點法來偵測何種 NMDA 接受器的亞型受影響。我們的結果顯示在嗎啡組出生後 14 天和控制組相比較， NR2A 有顯著的下降，但是 NR1 和 NR2B 在兩組間相比較並無意義；且在其他天數的 NMDA 接受器不同的亞型在兩組間相比較也無明顯差異。 PSD-95 (post-synaptic density 95) 是一種存在於突觸後神經元細胞質內的蛋白之一，已知 PSD-95 和 NR2A 彼此連結，具有穩定 NMDA 接受器的功能。然而我們發現嗎啡組海馬迴中 PSD-95 的蛋白表現量與對照組相比，並無差異。另外，嗎啡組其海馬迴中的突觸小泡膜蛋白 synaptophysin 表現量也無受到影響。總結上述，我們的結果證實在產前長期注射嗎啡的母鼠所生幼鼠海馬迴中之 NMDA 受體的減量調控現象,和突觸後 PSD-95 及突觸前 synaptophysin 的蛋白表現量並無相關。是否這些早期接受器量的改變，會阻礙海馬迴的神經發育，進而造成對學習和記憶的影響，這些待更進一步的長期研究。

Part II --中文摘要

過去研究報告指出，在吸食嗎啡或海洛因而成癮的懷孕婦女，其所生的嬰兒發現有新生兒戒斷症狀和神經生理功能的異常現象。Fluoxetine 是一種抑制血清素再吸收的藥物 (selective serotonin reuptake inhibitor；SSRI)，在臨床上是一種常見的抗憂鬱用藥。已經有研究學者發現，使用 fluoxetine 會明顯的減低由嗎啡成癮所誘導產生的活動度和敏感度之變化。在此，我們利用實驗室長期以來建立起的動物模式，予母鼠持續施打嗎啡讓其成癮且懷孕，直至幼鼠出生 5 天。觀察三種抑制血清素再吸收藥物，包括 fluoxetine、citalopram 和 clomipramine，對於由 naloxone 誘導出的幼鼠脫隱症狀之影響。我們的結果顯示，fluoxetine、 clomipramine 和 citalopram，皆能延長第一次出現腹

部強直的時間；降低腹部強直和打哈欠的頻率，且有 dose-dependent。根據我們的實驗結果，我們認爲未來在臨床上可以利用 SSRI 來治療新生兒對嗎啡成癮的戒斷症狀。

英文摘要

Part I

Our previous investigation revealed that rats born to dam rats chronically received morphine injection (morphine group rats) had a significant down-regulation of NMDA receptor in the hippocampus on postnatal day (PND) 14, but not on other examined PND. We further determined whether this down-regulation is specific for one of the subunit of NMDA receptor by using immunoblotting assay. The result showed that the NR2A, but not NR1 or NR2B, of morphine group rat was down-regulated on PND14, but not on PND30 or PND60 in the hippocampus of morphine group rats as compared to that of control rats. It is known that NR2A are linked to the anchoring protein, PSD95, on the post-synaptic density. However, we found that no change in the PSD-95 is associated with the down-regulation of NR2A. In addition, prenatal morphine treatment did not alter the expression of synaptophysin, a synaptic vesicle transmembrane protein in pre-synapse. To summary, these results demonstrated a transient down regulation of NR2A which is not associated with a change in the expression of PSD-95 and synaptophysin in the hippocampus of morphine group rats. Whether this early event in receptor alteration may hamper the development of neural function of hippocampus, such as learning and memory, in a long run require further explored.

Part II

It has been reported that infants born to morphine or heroin addicted women have high incidence of neonatal abstinence syndrome and abnormal neuropsychological performance. Previous studies had indicated that fluoxetine increasing serotonin (5-hydroxytryptamine, 5HT) transmission will attenuate morphine-induced locomotion and block morphine-sensitization. It is well-known that fluoxetine is a serotonin reuptake transpoter (SERT) inhibiter commonly used as antidepressants in clinics. In this study, we investigate the effect of fluoxetine and another two SERT inhibitors, citalopram and clomipramine, in attenuating naloxone precipitated-morphine withdraw syndrome in 5-day-old rats born to dams rats prenatally received daily morphine injections until 5 days post-delivery. Our data showed that fluoxetine、 clomipramine and citalopram can significantly increase latency of abdomen stretching, decrease frequency of abdomen stretching and yawn behavior in a dose-dependent manner in neonatal rats prenatally expose to morphine. This result suggests that SERT inhibitors could be of potential in clinics for treat in

the acute morphine withdraw syndrome in newborn baby.