• 系統編號	RN9705-2280
• 計畫中文名稱	產前長期暴露於嗎啡對幼鼠其發育中腦部血清素接受器表現及其下游 Glycogen Synthetase Kinase (GSK)活化的影響
• 計畫英文名稱	The Effect of Prenatal Exposure to Morphine on the Developmental Expression of Serotonin Receptor and the Down-Stream Activation of Glycogen Synthetase Kinase (GSK)
• 主管機關	行政院國家科學委員會
• 計畫編號	NSC95-2314-B038-059
• 執行機構	台北醫學大學醫學研究所
• 本期期間	9508 ~ 9607
• 報告頁數	8 頁
• 使用語言	中文
• 研究人員	-- --
• 中文關鍵字	血清素接受器; 新生幼鼠; 嗎啡; NMDA 接受器; 肝醣合成脢激脢
• 英文關鍵字	Serotonin receptor; Prenatal exposure; Morphine; GSK3 beta; ERK; Akt; PI3K; PP1, Neonatal rat
• 中文摘要	Glycogen synathasekinase-3 beta (GSK-3beta)是肝醣合成路徑中調節肝醣合成脢活性的一個磷酸激脢，但過去研究顯示 GSK-3beta 的活性在神經病理及發育中神經之軸突生長及細胞極性化(neuronal polarity)具極重要角色。磷酸化 GSK-3beta 會使之失去活性而此磷酸化作用是經由 PI3(phsophoinsitol-3 kinase)／Akt (protein kinase B)、extracellular signal-regulated protein kinase(ERK)的作用而其去磷酸化則是經由 protein phosphotase1 作用。嗎啡可藉由活化類鴉片接受器來調控 PI3K／Akt 路徑來調控 GSK-3beta 的磷酸化。我們過去研究發現由此顯示清素再吸收抑制劑 serotonin reuptake inhibitor)藥物能有效抑製出生幼鼠的嗎啡脫癮症狀。這些藥物之所以有療效其中一個可能性是產前長期暴露在嗎啡下會使得新生幼鼠腦部血清素神經傳導活性有異常下降。此變化也有可能是因血清素接受器的量發生變化。這包含主要的接受器如 5-HT1A、5-HT1B 、5-HT2A 及 5HT2B 。近年也發現血清素會對肝醣合成脢激脢(GSK-3beta)的活化產生調節影響。基於上述發現及推測，本研究計畫的目的是一、確定產前暴露於嗎啡之新生幼鼠其腦部是否有血清素接受器表現量改變；二、確定產前暴露於嗎啡之新生幼鼠其腦部是否有 GSK-3beta 之活化表現量的改變。一旦 GSK-3beta 之活化表現量有意義的改變我們將接續偵測與調控 GSK-3beta 活化之酵素即 PI3K、Akt、ERK 及 PP1 的活化狀態。本實驗將以西方點墨法定量幼鼠在一天、七天、十四天及三十天時各腦區(包括大腦皮質及海馬)中血清素接受器亞型(5-HT1A、5-HT1B、 5-HT2A、 5-HT2B)的表現量，並且也定量 GSK-3beta、 PI3K 、Akt 、ERK 及 PP1 的蛋白質及其磷酸化蛋白質的表現量。本計劃結果將有助於進一步瞭解嗎啡影響腦部神經發育的機制，並且提供未來在藥物治療上以選擇性 GSK-3beta 抑制劑在治療新生兒嗎啡戒斷後腦神經毒性的可能性的評估。

- 英文摘要

We previously have found that the naloxone-precipitated morphine withdrawal syndrome in neonatal rats, born to dams rats received daily injection of morphine since a week before mating till a week after delivery, could be attenuated by directly injection of serotonin reuptake inhibitor. This raises the possibility that prenatal exposure to morphine could alter the expression of the serotonin receptor or alter the activities of its down-stream biochemical pathways. Recent investigations have found that glycogen synthase kinase3 beta (GSK3beta) takes important role in the both neurophysiology and neuropathology, and it could be regulated by the activation of serotonin receptor. Activation of GSK3beta is dependent upon the status of phosphorylation, which is in turn regulated by the activation of PI3(phsophoinsitol-3 kinase)／Akt (protein kinase B), extracellular signal-regulated protein kinase (ERK)and phosphotase1. Therefore, in this project, we will determine whether prenatal exposure to morphine could alter the ontogenic expression of serotonin receptor, namely, 5-HT1A, 5-HT1B, 5-HT2A, 5-HT2B receptor and the expression of GSK3 beta, PI3K,Akt, ERK and PP1, and their phosphorylated forms in the cortex and hippocampus of rats with age of 1, 7, 14 and 30 days. The result will bring more understanding regarding the neurotoxic effect of morphine on the developing brain in term of serotonin receptor-mediated neurotransmission.