• 計畫中文名稱	探究薑黃素調節嗎啡耐受性的神經發炎機轉		
• 計畫英文名稱	--		
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• 中文關鍵字	薑黃素；嗎啡；藥物耐受性；發炎；細胞激素；趨化激素；興奮性胺基酸；穀胺酸轉運器；		
• 英文關鍵字	Curcumin；Morphine；Drug tolerance；Inflammation；Cytokines；Chemokines；Excitatory amino acids；Glutamte transporters；		
• 中文摘要	在許多情形中，嗎啡是處理嚴重急慢性疼痛最有效的藥物。然而，臨床上的使用 受限於它的副作用及嗎啡耐受性。嗎啡耐受性是一種神經發炎反應並會引起神經膠細胞 的活化以及釋放細胞激素等反應。有趣的是嗎啡耐受性與神經病理性疼痛這兩種看似不 相干的兩種神經發炎現象，卻透過共同的神經傳導物在 NMDA 接受器的層級產生交互作 用。穀胺酸轉運器可以調節興奮性胺基酸的活化所以對於 NMDA 接受器的活化也佔有具 足輕重的角色。此外，我們也曾經報告過治療這兩種現象的藥物通常可以交互的使用， 甚至是用同等的劑量。天然草藥萃取物如人蔘、印度人蔘及附子等曾經被研究用來降低 嗎啡耐受性的形成，近來也有文獻指出口服或是腹腔內注射薑黃素能夠有效的減輕由糖 尿病所導致的神經病理性疼痛，因此我們想使用薑黃素來減低嗎啡耐受性的程度。薑黃 素長久以來就被中醫入藥用來治療發炎性以及慢性疼痛且科學實驗已經證實許多有益 的作用，包括抗發炎、抗氧化，以及化學治療等等的效果，利用薑黃素抗發炎的效果來 治療嗎啡耐受性這種發炎現象是合乎常理的。 由上所述，薑黃素對於嗎啡耐受性的影響是值得被探討的，在這個實驗中嗎啡的 止痛作用是藉由 52 度 C 熱水浸潤試驗看閃尾的潛伏期來表示。我們利用小鼠先做 preliminary study 來看看薑黃素對於嗎啡耐受性的影響。在小鼠皮下注射每天每公斤 10 毫克的嗎啡來引發嗎啡耐受性。實驗設計包括幾個部分，首先，在單次注射部分，同 時給予薑黃素以及嗎啡後並每隔 15 分鐘連續觀察閃尾時間共計 90 分鐘來看薑黃素本身 是否會增強嗎啡的止痛作用。然後，在慢性給予部分，使用另一組小鼠連續七天皮下注 射嗎啡，然後每天在給藥後 30 分鐘測試閃尾時間。而薑黃素有幾種方式，包括與嗎啡 同時連續七天給予、前四天與嗎啡同時給予然後五至七天單獨給與嗎啡，或是在給予嗎 啡四天後，第五至第七天與嗎啡同時給予。慢性給予後第八天做累積劑量-反應曲線並 取得各組的 AD50。我們在 preliminary results 中發現薑黃		

	素對於嗎啡耐受性是呈現雙向 性的影響，也就是說低劑量的時候可以減少嗎啡耐受性而高劑量的時候反而加劇嗎啡耐 受性。實際實驗時我們將用大鼠重覆這個行爲的實驗，並比較不同劑量(低、中、高劑 量)薑黃素在嗎啡耐受性產生的過程中，對於腦脊髓液中興奮性胺基酸變化的影響。在 第八天採血並比較血清中細胞激素/趨化激素的變化，然後犧牲各組的老鼠以取得腰椎 脊髓背角部分做免疫螢光染色來分析相關之細胞激素/趨化激素的表現，並且看看穀胺 酸轉運器在嗎啡耐受性被改變後的表現。
• 英文摘要	Systemic administration of morphine is the most effective means of alleviating severe pain across a wide range of conditions. Its clinical use, however, has been limited by undesirable side effects, and tolerance. Morphine tolerance is a neuronal inflammatory process and may activate glial cell and induce release of cytokine/chemokines. Interestingly, morphine tolerance and neuropathic pain, two seemingly unrelated neuroinflammatory phenomena, may be interrelated by common neural substrates that interact at the level of NMDA receptor activation. Glutamate transporters, which regulate excitatory amino acids homeostasis, play important roles in the activation of NMDA receptors. Besides, we previously reported that the drugs for neuropathic pain and opioid tolerance are possibly interchangeable in some aspects and the dose could even be the same in certain condition. Natural herbal extracts, such as ginseng, Indian ginseng (Withania somnifera) and processed Aconiti tuber has been shown to attenuate the development of morphine tolerance. Recently, diabetic neuropathic pain has been reported to be successfully attenuated by curcumin, administered either orally or intra-peritoneally. Curcumin has long been used as an analgesic adjuvant in Chinese herbal medicine for inflammatory and chronic pain. Curcumin has a surprisingly wide range of beneficial properties, including anti-inflammatory,antioxidant, and chemotherapeutic activity. Utility of its potent anti-inflammatory effect to attenuate morphine tolerance is reasonable. From described above, we try to investigate the effect of curcumin on morphine tolerance. Tail-flick latency in 52℃ hot water immersion test will be used to determine morphine's antinociception. In preliminary studies, we tried to investigate the effect of curcumin on morphine tolerance in mice and 10 mg/kg morphine subcutaneously was to used to induce mrophien tolerance. The experimental design comprises several sections, including acute co-injection, chronic co-administration, and examining the underlying mechanism. Firstly, we try to elucidate if curcumin can enhance morphine's antinociception by acute injection in a 90-min time period. Secondly, regarding the chronic co-administration, different co-administration interval of curcumin will be tried during induction of morphine tolerance to see if curcumin could prevent or reverse the morphine tolerance. Preliminary results showed a biphasic effect of curcumin on morphine tolerance, which meant that curcumin attenuates morphine tolerance at low dose, but aggravates it at high dose. We plan to investigate the effect of curcumin on the release of CSF excitatory amino acids during the development of morphine tolerance. Furthermore, on day 8, serum cytokine/chemokines will be compared and corresponding changes also examined on dorsal horn of the spinal cord by immunohistological staining. Expression of glutamate transporter is also expected to be changed by different doses of curcumin during the development of morphine tolerance.