嗎啡強化活化劑引起血小板凝集反應的機轉探討

Mechanisms of morphine potentiated agonist-induced platelet aggregation in human platelets

中文摘要

嗎啡最早在十九世紀初被發現具有強力的止痛效果，用來緩解癌症末期病患的疼痛，且對處理某些重大的疾病、創傷及外科手術是必須的。至於嗎啡對人體血小板的影響如何？其機轉又爲何？近幾年來卻少有人討論，本篇論文主要的研究目的是詳細的進一步探討嗎啡作用在血小板上的機制。

在人體的血小板懸浮中，發現 morphine 能隨著濃度的增加而有效的強化由 collagen (1 g/ml)、U46619 (0.5 M) 所引起的血小板凝集及 ATP 釋放反應。morpine (1, 5 M) 能依劑量相關性的方式 (dose-dependent)，強化不同活化劑所引起的血小板凝集反應。另外，morphine 強化 collagen 所引起的 phosphoinositides (PI) 的分解，同時亦可促進 collagen 所引起的血小板細胞內 pH 值上升與鈣離子的增加及 thromboxaneB2 的形成。再者利用偵測血小板內 prostaglandin E2 的含量來代表 cyclooxygenase 活性時，發現 morphine 對 cyclooxygenase 的活性並沒有影響。接下來，利用 yohimbine (0.1 M) 會和血小板細胞膜上的 2-adrenoceptors 結合的特性，發現 morphine 在 Yohimbine 的存在下，無法強化 collagen (2 g/ml) 所造成的血小板凝集效果。這個實驗結果可能和 morphine 作用在血小板的 2-adrenoceptors 有關。

另一方面，嗎啡無法影響 FITC-triflavin 與血小板表面之 glycoprotein IIb/IIIa complex 的結合。Triflavin 是由 Trimeresurus flavoviridis 蛇毒中純化的的單鏈 peptide, 對血小板細胞膜的 GP IIb/IIIa 受體具有專一性的拮抗作用。 Morphine (1, 5 M) 能抑制血小板內由 prostaglandin E1 (10 M) 所引起的 cyclic AMP 的含量；另外利用 chemiluminesence 的方法進一步探討 morphine 對血小板中 NO 的影響，實驗結果發現 morphine 單獨存在下並不會增加 NO 的濃度。

綜合以上的實驗結果，發現 morphine 作用在血小板的機制可能爲透過 2-adrenoceptors 而抑制細胞內 cyclic AMP 的增加，並且增加細胞內鈣離子的釋放，經由 arachidonic acid 的路徑，造成 thromboxane B2 的含量增加，最後造成強化血小板凝集的結果。

英文摘要

The discovery of pharmacological activity of morphine early in the 19th century and the demonstration of its potent analgesic properties. Morphine had been used to relax the pain of cancer patients on the last phase , and dealed with some serious diseases、trauma and surgery was needed. However, how the influence of morphine on wash human platelets, and what are the mechanisms involved in this influence, it still remains unclear. Recently

the subject had not been discussed widely. The aim of this thesis is to further investigate the detailed mechanisms of morphine on human platelets.

In our studies, we found that morphine (1, 5 M) dose—dependently potentiated platelet aggeregation and ATP release by collagen (1 g/ml) and U46619 (0.5 in human platelet suspensions. Morphine (5 M) potentiated [3H inositol monophosphate formation stimulated by collagen (5 g/ml) in [3H myoinositol loaded platelets. Furthermore, morphine also potentiated [Ca2+]i mobilization in human platelet suspensions stimulated by collagen (1 g/ml). At the same dose, morphine significantly potentiated thromboxane B2 formation of collagen-activated platelets. Consequently, we measured prostagladinE2 formation as an index of cyclooxygenase activity. We found that morphine had no significant effect on cyclooxygenase activity, and found it did not potentiate collagen-induced platelet aggregation in the presence of yohimbine. According to these results, we found the effect of morphine on human platelets may be mediated via activation of adrenoceptors.

On the other hand, morphine (1, 5) inhibited prostaglandin E1 (10 induced cyclic AMP increase in human platelets. We examined this potentiation involved in platelet signal transduction system such as Na /H pump in human platelet suspensions. In contrast, morphine did not significantly increase nitrate formation in human platelets.

Moreover, we found morphine did not influence the binding of FITC-triflavin to platelet glycoprotein IIb/IIIa complex. Triflavin, an Arg-Gly-Asp-containing antiplatelet peptide, was purified from Trimeresurus flavoviridis snake venom.

Measurement of the platelet membrane fluidity, we found that morphine did not significantly affect the platelet membrane fluidity diphenylhexatriene (DPH)-loaded platelets .

Based on the above observations, we suggested that morphine may bind to adrenoceptors in human platelets, resulting in inhibition of cyclic AMP formation and concurrently increased intracellular Ca2+, resulting in activation of phospholipase A2 , and increased formation of thromboxane A2 formation, and potentiation of platelet aggregation.