懷孕婦女的血小板過度活化的機轉探討

Mechanisms of hyper-aggregability of platelets in normal pregnancy

中文摘要

在體內，懷孕婦女在整個懷孕期間血小板有明顯過度活化的情況發生，這種現象容易造成高凝血狀態，而使得懷孕婦女會產生一些併發症，例如血管性栓塞和瀰漫性血管內凝血。

在之前的體內實驗研究發現，懷孕婦女對於一些血小板的刺激劑有較高的敏度性，而造成懷孕婦女的血小板有過度活化的反應，其可能是經由透過thromboxane的生合成而來。

在本篇研究，我們利用ADP (20 mM)，collagen (1 mg/ml) 和thrombin (0.04 U/ml) 誘導血小板的凝集，來比較懷孕和未懷孕婦女血小板凝集的程度，發現懷孕婦女有較高血小板凝集的狀況發生。所以，我們懷疑懷孕婦女的血小板是否易作用在血小板凝集的最後共同路徑上；也就是纖維蛋白原 (fibrinogen) 與血小板細胞膜上的glycoprotein IIb/IIIa complex的結合，進而造成血小板的過度活化。實驗發現，懷孕婦女的血小板過度活化的反應可能與血小板細胞膜上的glycoprotein IIb/IIIa complex無關。

另外，利用collagen (10 mg/ml) 去誘導細胞內鈣離子的增加，懷孕婦女血小板細胞內鈣離子的濃度明顯著地增加，同時也增加了鈣離子的mobilization。再者，我們利用collagen (4 mg/ml) 去誘導血小板thromboxane A2 形成；實驗發現懷孕婦女thromboxane A2的量明顯地比未懷孕婦女來的高。進一步，我們藉由arachidonic acid (100 mM) 誘導prostaglandin E2的產生，發現懷孕婦女和未懷孕婦女兩者之prostaglandin E2的合成量並沒有什麼差別，此暗示著懷孕婦女的血小板過度活化可能不經由cyclooxygenase的路徑。另一方面，懷孕婦女cyclic AMP的量比未懷孕婦女低。而且在imidazole (600 mM) 和indomethacin (500 mM) 存在下阻斷thromboxane A2的生成，測量cyclic AMP的含量，發現懷孕婦女和未懷孕婦女其cyclic AMP的含量兩者間無意義差別。因此我們證實懷孕婦女的血小板是先經由增加thromboxane A2的含量，而導致cyclic AMP含量的下降。另外，懷孕婦女的血小板其由thrombin所引起的細胞內DpH值也明顯地比未懷孕婦女的血小板來的高，此結果暗示著是增加thromboxane A2的合成及降低cyclic AMP會明顯的促進細胞內pH值的鹼化作用。而利用chemiluminesence的方法進一步偵測懷孕婦女和未懷孕婦女對nitrate的含量，結果發現懷孕婦女造成血小板的過度活化可能與血小板釋放NO無關。

綜合以上結果可以得知，懷孕婦女血小板的過度活化反應其作用機轉可能是當血小板的活化劑 (如collagen, ADP, thrombin) 引發懷孕婦女的凝集反應後，

會進一步使得 thromboxane A2 的合成增加，thromboxane A2 含量的增加會抑制血小板細胞膜上 adenylate cyclase 的活性，而降低 cyclic AMP 的量，使得 Na+/H+ 交換增加，導致細胞內 DpH 值的增加，進一步促進細胞內鈣離子的增加，而使得懷孕婦女的血小板有過度活化的情況發生。

英文摘要

There are considerable evidences of platelet hyperaggregability in women during pregnancy in vivo. This may contribute to the hypercoagulation which occurs during pregnancy which may in turn play an important role in thromboembolism and disseminated intravascular coagulation.
Previous studies suggest that platelets from pregnancy women increased sensitivity to aggregating agonists via a thromboxane-dependent manner.
In this study, we found that platelet aggregation was significantly increased induced by ADP (20 mM), collagen (1 mg/ml) and thrombin (0.04 U/ml) in healthy pregnant platelet suspensions as compared with non-pregnant platelets. This may imply that pregnant platelets potentiate fibrinogen binding to fibrinogen receptor associated with the glycoproetin IIb/IIIa complex. However, we found that pregnant platelet suspensions did not significantly affect the FITC-triflavin binding to the glycoprotein IIb/IIIa complex.
In addition, collagen (10 mg/ml) induced intracellular [Ca2+] mobilization of pregnant platelets were markedly higher than non-pregnant platelets. Furthermore, our results also revealed that the levels of thromboxane A2 formation induced by collagen (4 mg/ml) in pregnant platelets were higher than non-pregnant platelets. In addition, we found that levels of prostaglandin E2 formation induced by arachidonic acid (100mM) in pregnant platelets did not differ from the non-pregnant platelets. On the other hand, we also found that the levels of cyclic AMP in pregnant platelets were less than non-pregnant platelets. By means of imidazole (600 mM) and indomethacin (500 mM) to inhibit thromboxane A2 synthesis, the levels of cyclic AMP both in pregnant and non-pregnant platelet suspensions were not significantly difference. Furthermore, thrombin-induced intracellular DpH change was markedly in pregnant platelets. It implies that inhibition of cyclic AMP may promote the Na+/H+ changer in human platelets. In contrast, the nitrate formation was not significantly different between pregnant and non-pregnant platelets.
These results indicate that the phenomenon of platelet hyperaggregability in pregnant platelets may initially induce the thromboxane A2 formation, resulting in inhibition of platelet membrane-associated adenylate cyclase, thereby lowering the cyclic AMP levels in platelets, followed by the increase of intracellular DpH, finally elevated the intracellular Ca2+ mobilization.