Atenolol 與 Carvedilol 於高血壓大白鼠大動脈內皮細胞隙連結之差異性作用

Distinct Effects of Atenolol and Carvedilol on Aortic Endothelial Gap Junctions in Hypertensive Rat

中文摘要

隙連結已知在協調相鄰的血管細胞，以維持內皮細胞的完整性及正常血管伸縮之反應上扮有重要的地位。我們之前的研究發現，高血壓大白鼠大動脈內皮細胞的隙連結會向下調節，此種調節是否會因爲降壓藥物的治療而改變未明。此外不同機轉的乙型交感神經阻斷劑，如 atenolol 及 carvedilol 已知對於因高血壓而受損的內皮細胞有不等程度的功能恢復，然而此種不同的功效是否亦影響內皮細胞隙連結之表現？這是本篇文章研究的目的。我們取 30 隻 3 個月大的成年雄性 Sprague-Dawley 大白鼠，在連續 8 週給予飲水中含有每公升 0.4 公克的 L-NAME 後，使其產生高血壓。最後一週再根據不同的投藥方法而平均分爲三組。第一組及第二組大白鼠除了持續飲用含有 L-NAME 之飲水外再分別以人工餵以 atenolol (每天每公斤 100 毫克)及 carvedilol (每天每公斤 50 毫克)；第三組僅繼續飲用含有 L-NAME 之飲水而不餵藥物。此外，第四組選取 10 隻年齡相當的雄性 Sprague-Dawley 大白鼠， 8 週中正常飲水且不給予任何藥物，來做爲對照組。當實驗終了，再應用免疫共軛焦雷射顯微鏡來檢視大動脈內皮細胞的連接素 37、40 及 43 之變化。結果顯示，第一及第二組相較於第三組而言，有較低的尾部袖壓(P 值均小於 0.01)；但相對於第四組而言，袖壓則較高(P 值均小於 0.01)。比較隙連結在各組的表現，如同之前的報告，第三組相較於第四組而言，連接素 37 的總面積減少 59%而連接素 43 減少 35% (P 值均小於 0.001)。而此種隙連結連接素的減少，可在大白鼠餵食一星期的 atenolol(第一組)或 carvedilol(第二組)後而改善：第一組相較於第三組連接素 37 增加 105%，而連接素 43 增加 30% (P 值均小於 0.01)；第二組相較於第三組連接素 37 增加 155%，而連接素 43 增加 61% (P 值均小於 0.001)。第二組相較於第一組而言有更佳的連接素表現(包括隙連結斑塊大小及總面積，P 值均小於 0.05)；甚至與第四組相當(P 值均大於 0.8)。相反地，連接素 40 在各組之間的表現都相似。綜合以上發現，即使在在血壓尚未完全降低至正常的情況下，大白鼠大動脈內皮細胞隙連結之向下調節的現象，可因短期 atenolol 及 carvedilol 的治療而部份或全部改善。這意指經過降壓壓物治療後，內皮細胞隙連結的恢復速度可較血壓的降低來得快。此外，不同的降壓藥物對於內皮細胞隙連結有差異性的調節作用，表示除了單純降壓的效果之外，降壓藥物還可因其獨特的藥理特性來調節內皮細胞的隙連結。上述發現讓我們對於現存降壓藥物有了重新醒思，除了單純降壓的效用之外，更應著重於其對於內皮細胞功能的早期恢

復。

英文摘要

Gap junctions have been known to play a major role in the maintenance of integrity of endothelium and coordination of vasomotor responses between adjacent vascular cells. Our previous work found that aortic endothelial gap junctions are down-regulated in hypertensive rats. Whether such a down-regulation is altered by hypotensive drugs remains unknown. Atenolol and carvedilol, two β-blockers with differential intrinsic properties, are reported to have distinct potential to correct endothelial dysfunction in hypertension. We aim to clarify whether such a diverse effect in restoration of endothelial function involves the regulation of gap junctions. Thirty adult male Sprague-Dawley rats (3 months old) were made hypertensive by adding L-NAME (0.4 g/L) in the drinking water for 8 weeks. In the last week of L-NAME giving, the animals were equally divided into 3 groups. Groups 1 and 2 received either atenolol (100 mg/kg/day) or carvedilol (50 mg/kg/day), respectively. Group 3 did not take any hypotensive drugs. Another 10 age-matched rats receiving neither L-NAME nor hypotensive drugs were designated as Group 4. At the end of experiments, the expression of aortic endothelial connexin37 (Cx37), Cx40, and Cx43 was examined by en face immunoconfocal microscopy. The results showed that tail-cuff pressure in both Groups 1 and 2 is significantly reduced, compared to Group 3 (both $p < 0.01$); but higher, compared to Group 4 (both $p < 0.01$). Gap junctions, as previous reported, are less abundant in Group 3, compared to Group 4 (Total gap-junctional area: Cx37, 59% and Cx43, 35% reduction; both $p < 0.001$). The reduction is attenuated after treatment with atenolol (Group 1 vs Group 3: Cx37, 105% and Cx43, 30% increment; both $p<0.01$). Treatment with carvedilol leads to a more expression of both connexins (Group 2 vs Group 3: Cx37, 155% and Cx43, 61% increment; both $p<0.001$), to a level more abundant than Group 1 (for each of Cx37 and Cx43; both $p<0.05$) and equivalent to that of Group 4 (for each of Cx37 and Cx43; both $p>0.8$). Cx40, on the contrary, remains stationary between each of the groups. In summary, down-regulation of aortic endothelial gap junctions in hypertensive rats induced by L-NAME is partially recovered by a short-term treatment of atenolol but fully recovered by carvedilol even though the level of blood pressure is not lowered down to a normal level; this suggests that in hypertension state the normalization of endothelial connexins by hypotensive drugs may happen when blood pressure is not rigorously controlled. In addition, the differential regulation of endothelial connexins by different drugs suggests that intrinsic properties other than pressure-lowering effects of hypotensive drugs affect the expression of endothelial gap junctions. These novel findings inspire us to a reconsideration of hypotensive medicines in restoration

of endothelial function beyond the simple lowering effect of blood pressure.