行政院國家科學委員會專題研究計畫成果報告

Preparation of NSC Project Reports

† 八十六年度及以前的一般國科會專題計畫(不含產學合作研究計畫)亦可選擇適用，惟較特殊的計畫如國科會規劃案等，請先洽得國科會各學術處同意。

心電生 理特性、抗心律不整效力及不整脈誘發性之測定，包括carvedilol及thalidoparhine與liriodenine等新衍發物

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主持人：吳美環　台大醫學院小兒科

一、中文摘要

1. Carvedilol，一種所謂"第三代β-拮抗劑"，對對於心衰竭之長期療效已經多數臨床試驗證實。其機轉目前被認為是抑制因心衰竭引起自主神經過度代償之影響，且由於其α-拮抗效果，可使在急性期投藥時，藉α-拮抗引起之血管阻力下降，使病人之心衰竭不致惡化，因此此種α與β拮抗比率應可藉作長期抗心衰竭藥物設計之參考。
2. 本實驗室工作群長期致力於由天然植物萃取有效之化合物。經評估後，目前有兩大類化合物，一為thalidiporphine，一為liriodenine，兩者皆具有適宜之心肌收縮促進效果及抗心律不整效力。
3. 因此本群體計劃之目的在(1)將此兩大類化合物予以改變部份結構，使具有部份α與β拮抗作用(2)且能維持充份之心臟收縮促進效果及抗心律不整效力。
4. 本子計劃之主要工作在執行(1)第一年：先界定carvedilol是否有直接抗心律不整效力，或對心臟電生理特性有直接影響，若有，其機轉為何?(2)其次，第二年：將予界定thalidoporplinie各類衍生物之抗心律不整之效力及對心臟傳導系統之影響(3)第三年：將予界定liriodenine各類衍生物之抗心律不整之效力及對心臟傳導系統之影響。
5. 方法：(1)心臟電生理特性之評估：以Langendorff灌流之離體心臟作評估，以自製特別之電極導線放入心房、心室及希氏束處，記錄並刺激，以得到各項組織之電生理特性資料(2)抗心律不整之效力檢定：以Langendorff定壓灌流之模式，經綁住再放鬆左冠狀動脈支以誘發ischemia-reperfusion不整脈，比較carvedilol 及其他衍生物pretreatment或treatment與control之差異。
6. 第一年計劃結果顯示：結果顯示Carvedilol確能直接改變心電生理特性，可縮短房室結之傳導及心室組織之抑阻期。對於再灌流不整脈之誘發概率亦能略減少(100%降到81%)。此外並能停止再灌流不整脈，但最多只有50%效力(1.5μM與5.4μM皆然)。

二、ABSTRACT

Background. Two compounds, thalidoporphine and liriodenine, had been identified with an antiarrhythmia potential and

a low negative inotropy from our team. Further modification of the prototype will refer to a "third generation" ß blocking agent, carvedilol, that at therapeutic doses blocks all three adrenergic receptors, with a rank order of potency of $_{ß1}$> a$_1$ > $_{ß2}$. Because of its a-blocking effect, carvedilol is a moderate vasodilator on acute administration and therefore has a good initial tolerability in patients with heart failure. Besides, carvedilol has been shown as a strong antioxidant. The clinical efficacy had been well shown several clinical trials.

Methods. The direct modification by various interventions on cardiac conduction system was performed by intracardiac recording and stimulation in isolated, Langendorff perfused hearts. The and proarrhythmic potential was assessed by the incidence of ischemia /reperfusion arrhythmias after various interventions.

Results. Carvedilol may directly shorten progressively the conduction through the AV node as well as the ventricular refractory period (1.5 and 4.5 mM). However, theses changes were irreversible as compared to the time-control data. As to the conduction through the atrial, His-Purkinje system and their refractoriness were not significantly modified by carvedilol. Carvedilol can modestly convert the ventricular tachyarrhythmias induced by ischemia-reperfusion. At 1.5 mM and 4.5 mM, carvedilol could covert half of the reperfusion arrhythmias. Pretreatment by carvedilol (1.5 or 4.5 mM) could decrease the incidence of reperfusion arrhythmias from 100% (5/5) to 81% (9/11).

Conclusions. Direct electropgysiological effects of carvedilol and the potential of ameliorating ischemia-reperfusion arrhythmias had been documented. However, the antiarrhythmic potential related to the direct carvediolol electrophysiological effects may be weak. Clinical therapeutic potential of carvedilol may be more closely related to the ß blocking as well as a-blocking

三、緣由與目的

Medical treatment for the heart failure usually include: digoxin, diuretics, angiotensin converting enzyme inhibitor and phosphodiesterase. In recent years, research has been directed toward the understanding of the pathological mechanisms involved in the progression of congestive heart failure. Much of this research has focused on the various neuroendocrine systems that are activated in this syndrome and the roles they play in the progression of congestive heart failure.[1-2] The activation of neurohumoral pathways which lead to peripheral vasoconstriction and then enhances the afterload. Furthermore, the down-regulation of ß-receptor in the presence of chronic heart failure and the possible "catecholamine cardiotoxicity" prompted the rational of ß-blocker for chronic heart failure.[3-4] Several recent multicenter double blind, placebo-controlled clinical trials have proved the clinical benifits of carvedilol, a "third generation" ß-blocking agent. Carvedilol, at therapeutic doses, blocks all three adrenergic receptors, with a rank order of potency of $_{ß1}$> abol"###$_1$ > $_{ß2}$.[7] Because of its abol"###-blocking effect, carvedilol is a moderate vasodilator on acute administration and therefore has a good initial tolerability in patients with heart failure.[5] Besides, carvedilol has been shown as a strong antioxidant.[6] Clinical benefits have been well documented in patients with chronic heart failure from several multicenter clinical trials and hence carvedilol had been approved for the treatment of heart failure.[7-10]

In our team, we have identified several novel compounds derived from natural alkaloids which possess adequate positive inotropic effects and antiarrhythmia efficacy.[11-13] The positive inotropic effect is independent of adrenergic stimulation

and is attributed to the relative degree inhibition of I_{to} and I_{Ca}. The ionic current inhibition include mainly the I_{to}, I_{Na} and partly I_{Ca}. Via the inhibition, the electrophysiological properties of the cardiac conduction system are modified and consequently may terminate the arrhythmias. Therefore, such compound will be potential drugs for the treatment of arrhythmia and heart failure. However, based on the clinical experiences that the differential blocking effects on various sympathetic receptors, such as carvedilol, provide chronic benefits for heart failure. Our further aim for such drug development will be the modification of these compounds to contain the structure bone with various abol"###- and ß-receptor blockade and optimally antioxidation effects. Then, we may have the chance to obtain the ideal novel anticongestive drug; acutely and chronically positive inotropic and antiarrhythmic.

After the initial tests for the positive inotropic effects by muscle-strip experiment and neurotransmitters blocking assessment, the index compound will be identified. Then, the assessment of these compounds will include 1) electrophysiological properties of cardiac conduction system, 2) antiarrhythmia efficacy and 3) proarrhythmia potential.

四、結果

1. Direct electrophysiological effects

Carvedilol can cause progressively shortening of the conduction through the AV node. The ventricular refractory period was also significantly shortened (1.5 and 4.5 mM). However, theses changes were irreversible. (Table 1) As to the conduction through the atrial, His-Purkinje system and their refractoriness were not significantly modified by carvedilol

2. Antiarrhythmic effects (Ischemia-reperfusion model

A). Carvediolol: Carvedilol can modestly convert the ventricular tachyarrhythmias induced by ischemia-reperfusion. Carvedilol at 0.5 mM failed to convert the tachyarrhythmias , at 1.5 mM, carvedilol converted one out of two induced tacharrhythmias and at 4.5 mM carvedilol could only convert 3 out of 6 induced ventricular tachyarrhythmias.

B) Pretreatment by carvedilol (1.5 or 4.5 mM) could decrease the incidence of reperfusion arrhythmias from 100% (5/5) to 81% (9/11) (No statistical significance).

3. Proarrhythmic potential: No tachyarrhythmias or bradyarrhythmia had been induced during infusion of carvedilol (0.15, 0.5, 1.5 or 4.5 mM)

討論

Direct electrophysiological effects had been shown in this study. However, the electrophysiological modulation might not provide adequate antiarrhythmic effects. A prolongation of the refractoriness of the cardiac tissue had been suggested to be a common phenomenon for most antiarrhythmic agents. As shown in this study, the refractoriness of the cardiac tissue was not prolonged by carvedilol. The ventricular refractory period was even shortened. Therefore, the antiarrhythmic efficacy which was only fair may be related mechanisms other than electric modulation. Similarly, pretreatment with carvedilol also protected the hearts only weakly against the development of ischemia-reperfusion arrhythmia. The clinical therapeutic potentioal of carvedilol

may be more closely related to the ß blocking as well as a-blocking The potential compound developed from this team possesses antiarrhythmia efficacy and positive inotropy. Further modification of the potential compounds from this team will focus on the promotion of the ß- and abol" ###- blocking effects. Further quantification of the direct cardiac effects of carvedilol in chronic heart failure animal model (Hamster).may be helpful be fully elucidate the electrophysiological modulation by carvedilol in chronic heart failure.

REFERENCES

1. Cohn JN: Overview of pathophysiology of clinical heart failure. In: Congestive heart failure. Hosenpund JD, Greenberg BA (Eds). Springer-Verlag: Berlin 1994, 11-6.
2. Cohn JN, Rector JS: Prognosis of congestive heart failure and predictors of mortality . Am J Cardiol 1988;62:25A-30A.
3. Waggstein F, Caidahi K, Wallentin I, Bergh CH, Hjalmarson A: Long-term ß-blockade in dilated cardiomyopathy. Circulation 1989;80:551-563.
4. Rosenbaum JS, Ginsburg R, Billingham ME, Hoffman BB: Effects of adrenergic receptor antagonists on cardiac morphological and functional alterations in rats harboring pheochromocytoma. J Pharmacol Exp Ther 1987;241:354-360.
5. Ruffulo RR, Gelai M, Heible JP, Willette RN, Nichols AJ. The pharmacology of carvedilol. Eur J Clin Pharmacol 1990;38:S82-S88.
6. Yue TL, Cheng HY, Lysko PG, McKenna PJ, Feuerstein R, Gu JL, Lysko KA, Davis LL, Feuerstein G. Carvedilol, a new vasodilator and beta-adrenoceptor antagonist, is and antioxidant and free radical scavenger. J Pharmacol Exp Ther 1992;263:92-98.
7. Colucci WS, Packer M, Bristow MR, Gilbert EM, Cohn JN, Gowler MB, Krueger SK, Hershberger R, Uretsky BF, Bowers JA, Sackner- Bernstein JD, Young ST, Holcslaw TL, Lukas MA: Carvedilol ingibits clinical progression in patients with mild symptoms of heart failure. Circulation 1996;94:2800-2806.
8. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, Shusterman NH: The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. N Engl J Med 1996;334:1349-1355.
9. Bristow MR, Gilbert EM, Abraham WT, Adams KF, Fowler MB, Hershberger RE, Kubo SH, Narahara KA, Ingersoll H, Krueger S, Young S, Shusterman N: Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. Circulation 1996;94:2807-2816.
10. Australia/New Zealand heart failure research collaborative group. Randomised, placebo-controlled trial of carvedilol in patients with congestive heart failure due to ischaemic heart disease. Lancet 1997;349:375-380.
11. Wu MH, Su MJ, Lee SS, Lin LT, Young LT: Electrophysiogical basis for antiarrhythmia efficacy, positive inotropy and low proarrhythmic potential of (-)-caryachine. Br J Pharmacol 1995;3211-3218.
12. Chang GJ, Wu MH, Wu YC, Su MJ: Electrophysiological mechanisms for antiarrhythmic efficacy and positive inotropy of liriodenine, a natural aporphine alkaloid from Fissistigma glauscens. Br J Pharmacol 1996;118:1571-1583
13. Wu MH, Su MJ, Lee SS, Young LT: The electrophysiogical effects and antiarrhythmic potential of a secoaporphine-N-allylsecoboldine. Br J Pharmacol 1994;113:221-227.
14. Wu MH, Su MJ, Lue HC: Age-related quinidine effects on ionic currents of rabbit cardiac myocytes. J Mol Cell Cardiol 1994;26:1167-1177.