行政院國家科學委員會專題研究計畫進度報告

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thalidoporphine與liriodenine等新衍發物

Second year: Electrophysiological modulation by thlidophorphine

計畫編號：NSC 88-2314-B-002-019-M48
執行期限：88 年 8 月 1 日至 89 年 7 月 31 日
主持人：吳美環　台大醫學院小兒科

一、中文摘要

1. 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。
2. 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。
3. 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。
4. 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。
實驗：(2) 動物：一般正常hamster及心衰竭品種hamster。
5. 第二年計劃結果顯示：結果顯示心衰竭hamster的心臟傳導系統有顯著房室結之傳導延長現象，其AH間距由44±3延長到56±4ms，而wenckrbach週期由149±9延長到195±13ms。而若在實驗前每天投予thalidoporphine 4.5mg/day則可有效縮短這些延長現象。此外，thalidoporphine pretreatment能有效延長心房的refroctory period。然而不論是正常或心衰竭hamster的離體灌流心臟，thalidoporphine皆能有效依劑量成正比的延常房室結的傳導與refractoriness。

6. **推論：**thalidoporphine**能改善心衰竭心臟電氣傳導性質，然而這些影響與**thalidoporphine**的直接心臟效果並不盡然相同，自主神經系之調節或抗氧化的作用是必須考慮的機轉。**

二、ABSTRACT

Background. We have identified the compound, thalidoporphine, to possess an antiarrhythmia potential and a low negative inotropy.

Methods. The direct modification by various interventions on cardiac conduction system was performed by intracardiac recording and stimulation in isolated, Langendorff perfused hearts. The changes were measured in the hearts isolated from normal and cardiomyopathic hamster.

Results. As compared to the normal hamster, the failing heart isolated from the cardiomyopathic hamster showed significantly prolongation of the conduction through the AV node as well as the refractoriness of the AV node (AH interval was 44±3 in normal and 56±4 ms in the failing hearts. The Wenckebach cycle length was 149±9 ms in normal and 195±13 ms in the failing hearts). Pretreatment by thalidophorphine (4.5 μg/day) improved the conduction. The AH interval was shortened to 48±2 ms and the Wenckebach cycle length was shortened to 176±6 ms. There was no significant differences in the conduction and refractory period of the atrial and ventricular tissue between the normal and heart failure hamster. However, pretreatment by thlidophorine would increase the atrial refractory period. (the atrial effective refractory period was 45±3 in normal, 41±4 in failing hearts and 54±7 ms in the thlaidophorine group). No arrhythmia could be induced by programmed pacing in any of the 3 groups. However, thlidoporphine still could prolong the conduction through the AV node, the refractory period of the atrial and ventricular tissue dose-dependently in both normal and failing hearts of cardiomyopathic hamsters.

Conclusions. Failing heart of the cardiomyopathic hamster was characterized by a prolongation of conduction and refractory period of the AV node, which could be improved by pretreatment by thlidoporphine. Nonetheless, thalidoporphine could prolong the AV conduction and refractory period of the atrial and ventricular period of the cardiomyopathic hamster and normal hamster.

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. 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. Several recent multicenter double blind, placebo-controlled clinical trials have proved the clinical benefits of carvedilol, a "third generation" ß-blocking agent. Carvedilol, at therapeutic doses, blocks all three adrenergic receptors, with a rank order of potency of $\beta_1 > \alpha_1 > \beta_2$. Because of its α_1 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. 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.

In our team, we have identified several novel compounds derived from natural alkaloids which possess adequate positive inotropic effects and antiarrhythmia efficacy. 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 á and â- 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, thalidophorphine, had been identified.

We have identified the compound, ***thalidoporphine***, to possess an antiarrhythmia potential and a low negative inotropy. This second-year project sought to determine the direct electrophysiological modulation in normal and failing hearts of the hamster.

四、方法與結果

Methods. The direct modification by various interventions on cardiac conduction system was performed by intracardiac recording and stimulation in isolated, Langendorff perfused hearts. The changes were measured in the hearts isolated from normal and cardiomyopathic hamster.

Results. As compared to the normal hamster, the failing heart isolated from the cardiomyopathic hamster showed significantly prolongation of the conduction through the AV node as well as the refractoriness of the AV node (AH interval was 44±3 in normal and 56±4 ms in the failing hearts. The Wenckebach cycle length was 149±9 ms in normal and 195±13 ms in the failing hearts). Pretreatment by thalidophorphine (4.5 μg/day) improved the conduction. The AH interval was shortened to 48±2 ms and the Wenckebach cycle length was shortened to 176±6 ms. There was no signifcant differences in the conduction and refractory period of the atrial and ventricular tissue between the normal and heart failure hamster. However, pretreatment by thlidophorine would increase the atrial refractory period. (the atrial effective refractory period was 45±3 in normal, 41±4 in failing hearts and 54±7 ms in the thlaidophorine group). No arrhythmia could be induced by programmed pacing in any of the 3 groups. However, thlidoporphine still could prolong the conduction through the AV node, the refractory period of the atrial and ventricular tissue dose-dependently in both normal and failing hearts of cardiomyopathic hamsters.

五. 討論

Failing heart of the cardiomyopathic hamster were characterized by a prolongation of conduction and refractory period of the AV node. This may be related to altered I_{ca} and I_{to} in the failing hearts. However, such changes could be improved by pretreatment by thlidoporphine. However, thalidoporphine

could directly prolong the AV conduction and refractory period of the atrial and ventricular period of the hearts isolatedfrom cardiomyopathic hamster and normal hamster. The diverse effects between the pretreatment and treatment with thalidoporphine need to further clarified. The possibility of adrenergic modulation or antioxidant effects is suspected.

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.