行政院國家科學委員會專題研究計畫　成果報告

傳統中藥丹蔘純化物丹蔘酮降血壓機轉的研究

計畫類別：個別型計畫
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計畫主持人：陳保羅
共同主持人：徐鳳麟
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行政院國家科學委員會補助專題研究計畫 ■ 成 果 報 告
□期中進度報告

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計畫參與人員：

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執行單位：台北醫學大學萬芳醫院心臟內科

中　華　民　國　九十四　年　十　月　一　日

壹、中、英文摘要及關鍵詞(keywords)

一、中文摘要

關鍵詞：丹蔘酮，中草藥，高血壓大白鼠

高血壓是導致心血管疾病最常見的重要危險因子。雖然治療高血壓的西藥發展蓬勃，然而有效接受藥物治療高血壓人口約只有 25%，部份原因是因為西藥的副作用。所以如何從天然中草藥純化物發展為降血壓藥，一直是值得研究的課題。

丹蔘（Dan Shen 或 Tan Shen）在中藥使用治療心血管疾病已有數百年歷史，丹蔘抽取物證實在動物可降血壓，但其真正作用機轉未明。本計劃的研究目的，欲證明丹蔘萃取物－丹蔘酮(Tashinones)是否具有降低高血壓的效果。

本研究使用之丹蔘酮（Tashinones）由台北醫學大學生藥所所長徐鳳麟教授提供。動物實驗中，利用 Tashinones，在清醒的自發性高血壓大白鼠(SHR)，以腹腔注射的方式給予 20-60 mg/kg，發現在給藥 30 分鐘後，老鼠的血壓明顯下降，並且降低高血壓的效果可長達九十分鐘，而 Tashinones 在降低高血壓的效果呈現劑量相關性增加。另外在血壓正常的老鼠上，Tashinones 並不具有降低血壓的效果。根據本研究結果顯示，Tashinones 具有良好的降低高血壓的效果。

二、英文摘要

Keywords: Tashinones, SHR, Traditional herbs

Chronic essential hypertension is a major and the most common risk factor for developing cardiovascular disease. Despite the recent advancement in conventional drug therapy, compliance with antihypertensive drugs is still a common problem due to side effects. So it is still significant in the development of new antihypertensive drugs from natural products or traditional herbs.

Tashinones are purified from the dry root of *Salvia miltiorrhiza* Bge. (Labiatae), they are diterpene quinones isolated by Prof. Feng-Lin Hsu of the Graduate Institute of Pharmaconogsy of Taipei Medical University. In this study, we applied three doses, 20, 40 and 60 mg/kg of Tashinone on conscious spontaneous hypertensive rat (SHR). Thirty minutes after intraperitoneal injection of Tashinone, it decreased the blood pressure (BP) and the effects maintained for 90 minutes. Tashinone decreases the blood pressure in SHR in a dose-dependent manner. On the other hand, Tashinone didn’t change the BPs of normotensive rats (WKY). These data suggested that Tashinone is an effective anti-hypertensive drug.

貳、報告內容

一、前言

Hypertension is one of the most important modifiable risk factors for coronary heart disease (the leading cause of death in the United States and many European nations), stroke (the third leading cause), congestive heart failure, end-stage renal disease, and peripheral vascular disease（1-4）. Improvements in the identification and treatment of hypertension have contributed to a major reduction in the incidence of cardiovascular disease in many countries（5,6）. Despite these advances in the detection and pharmacologic treatment of hypertension, inadequate blood pressure control continues to be a major public health problem（7）. Compliance with antihypertensive therapy may be an important barrier to optimal blood pressure control, as some antihypertensive drug treatments can have a negative impact on quality of life (QOL) （8,9）. Development of new antihypertensive agents that have good efficacy and tolerability and also could be regarded as natural products would be of considerable clinical interest, particularly in Oriental countries, where herbal preparations are viewed favorably by patients.

Injection of Tan Seng extract into the isolated heart of guinea pigs or rabbits (normal or atherosclerotic) caused relaxation of coronary vascular smooth muscle and an increase in coronary circulation. In anesthetized dogs, the intravenous injection of Tan Seng extract in a dose of 4 g/kg increased coronary flow by 70.5％ and reduced resistance by 46％. Clinical trials with this extract in patients with coronary artery disease reported a definite increase in coronary circulation index (10).

The herb has a protective effect in acute myocardial ischemia. In experiments with animals in which myocardial ischemia was induced either by intracardial injection of norepinephrine (NE) or by partial ligation of a coronary branch, administration of *Tan Seng* extract reduced ischemic symptoms, improved the pathological electrocardiogram (ECG) pattern, and stimulated the regeneration of myocardial tissue. Tanshinone IIA, one of the active ingredients of the herb, and its water-soluble sulfonate salt were used clinically and showed an acceleration of coronary blood blow and collaterals by blocking Ca^{2+} entry（10）.

Tan Seng extract can dilate peripheral blood vessels, resulting in a drop in blood pressure. The effect can be blocked by atropine. Howevey, Tan Seng extract cannot reduce hypertension induced by norepinephine（10）.

二、研究方法

1. Animals

Male spontaneously hypertensive rats (SHRs, 350-450 g) and male Wistar-Kyoto rats (WKY) or Wistar rats (350-450 g) were used. They were obtained from the animal center of the National Cheng Kung University Medical College. Rats were housed in a temperature-controlled room (25±1℃) and kept on a 12hr : 12hr light-dark cycle (light on at 0600 h). Food (Purina Rat Chow) and water were available *ad labitum* throughout the experiment.

2. **Measurement of systemic blood pressure**

The systemic blood pressure was measured by a noninvasive tail-cuff monitor (UR-5000, Ueda Company, Japan) in conscious SHRs. The systolic blood pressure and heart rate of SHRs

can be recorded simultaneously. The SHRs (n=8), which had mean blood pressure higher than 160 mmHg were used to evaluate the antihypertensive activity of drugs. When the blood pressure was stable (varied less than 5 mmHg between 20 minute intervals), 20-60 mg kg^{-1} Tashinones (dissolved in normal saline) were administered intraperitoneally into SHRs. Other group of SHRs (n=8) received the same volume of normal saline as control. The systolic blood pressure was measured repeatedly 30,60,90 and 120 minutes after the injection of tashinones.

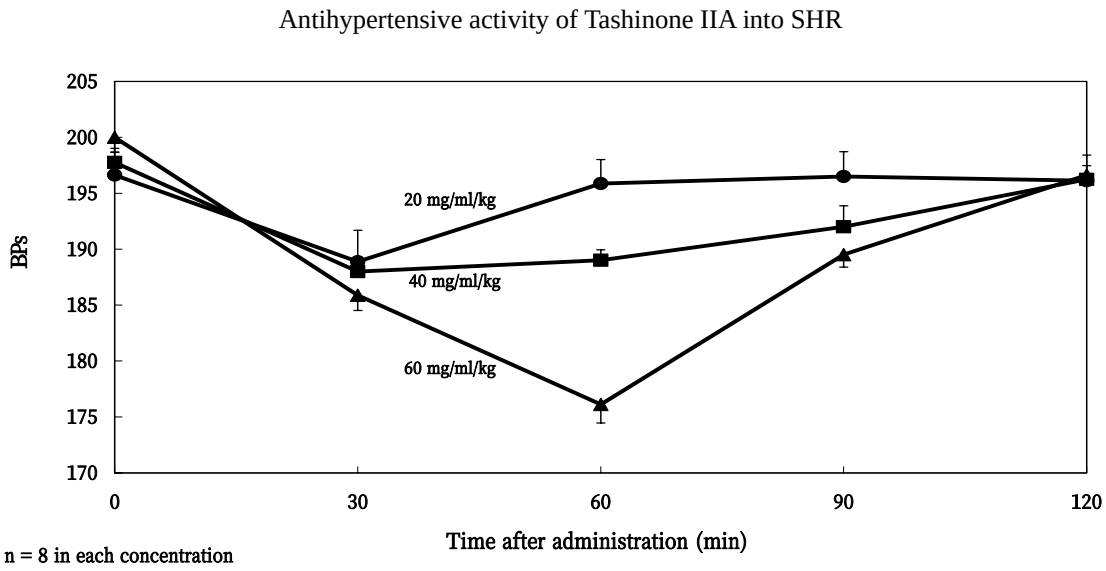
3. Statistics

All values were presented as mean ± standard error of mean. All experimental animal groups or experiments were 8 unless specified. ANOVA and Dunnetts post-hoc test was used to evaluate data between different experimental groups. A p value less than 0.05 was regarded as significant.

四、結果與討論

1. 丹蔘酮（Tashinone IIA）可降低高血壓老鼠(SHR)的血壓

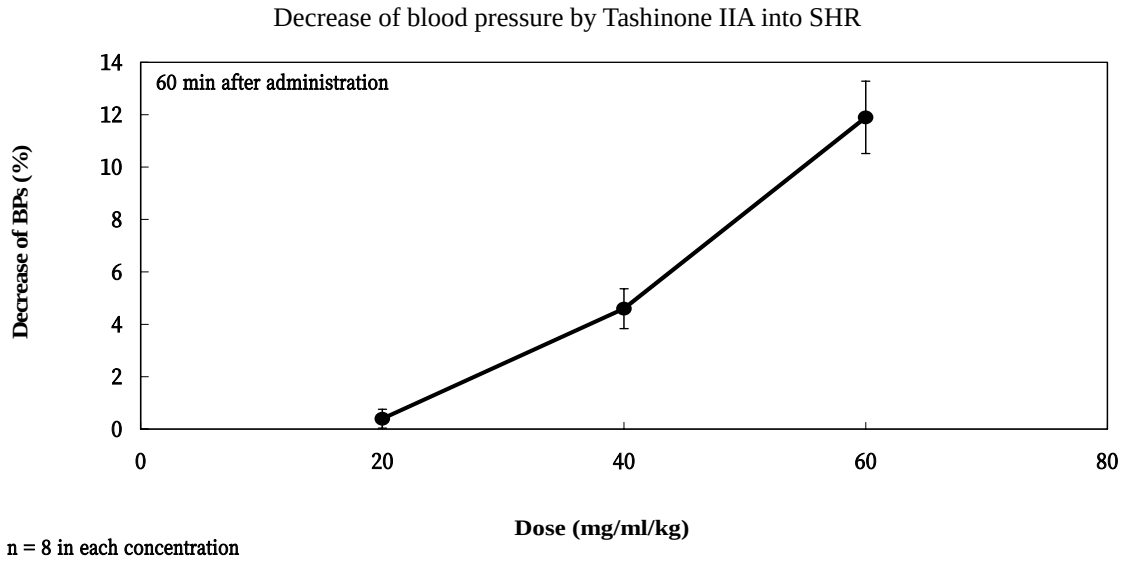
在高血壓老鼠(SHR)的血壓量測實驗中，我們給予 SHR 三種不同劑量的丹蔘酮，分別為 20 mg/ml/kg、40 mg/ml/kg 以及 60 mg/ml/kg，並且分別在給藥後的 30、60、90 及 120 分鐘測定老鼠的血壓。結果發現：在給藥三十分鐘之後，給予三種劑量的 SHR 的血壓即有明顯下降的情況；給藥後六十分鐘，給予 60 mg/ml/kg 的 SHR 降血壓的效果最佳，可降低約 12%；丹蔘酮降低 SHR 血壓的效果可達九十分鐘，各組老鼠的血壓在給藥後的 120 分鐘恢復原狀。(圖一)



圖一

2．丹蔘酮降血壓的劑量相關性試驗

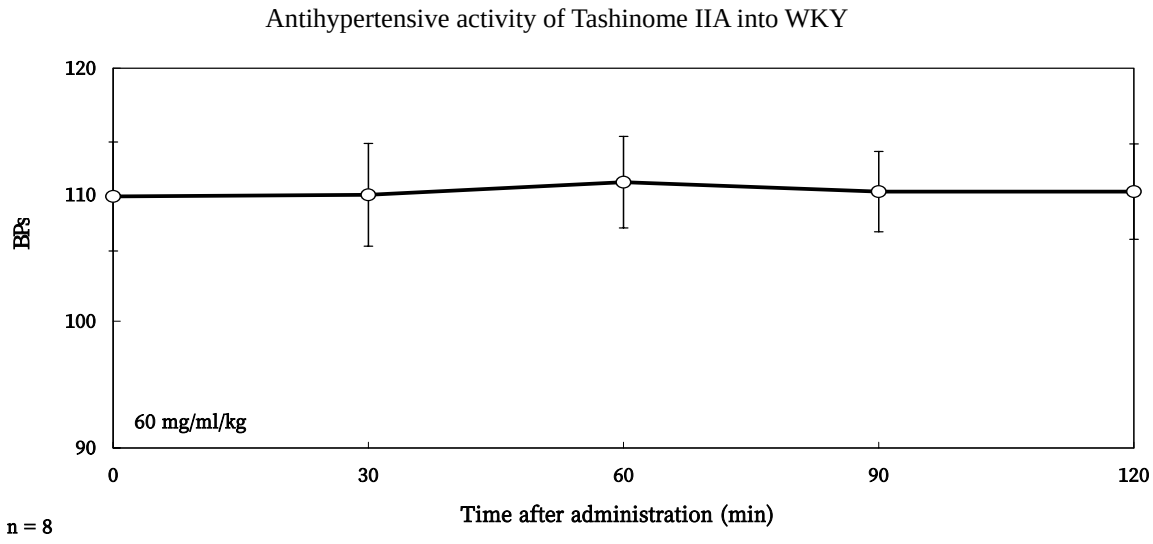
高血壓老鼠接受三種不同劑量丹蔘酮注射後的六十分鐘，分別測定其血壓，並記錄其血壓降低的情況，結果發現：隨著給予劑量的增高，SHR 血壓降低的百分比有隨之升高的情形，即丹蔘酮有劑量相關性的降低高血壓效果。(圖二)



圖二

3．丹蔘酮對正常老鼠的血壓影響

本研究使用血壓正常的 WKY 品系老鼠作為對照組實驗，在給予 WKY 老鼠 60 mg/ml/kg 之後的 30、60、90 及 120 分鐘測定老鼠的血壓，結果顯示：接受丹蔘酮注射的 WKY 老鼠血壓不會受到影響，可以維持正常狀態的血壓，由此結果可知丹蔘酮的降血壓作用只出現在高血壓狀態的老鼠，但不會影響正常老鼠的血壓。(圖三)



圖三

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