行政院國家科學委員會補助專題研究計畫成果報告

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※葉酸治療對於高同胱氨酸血症下腦血管反應性的影響※

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計畫類別：■個別型計畫　　□整合型計畫
計畫編號：NSC　90－2314－B002－229
執行期間：　90　年 08 月 01　日至 91　年 07 月 31 日

計畫主持人：趙嘉倫
共同主持人：
計畫參與人員：

本成果報告包括以下應繳交之附件：
- □赴國外出差或研習心得報告一份
- □赴大陸地區出差或研習心得報告一份
- □出席國際學術會議心得報告及發表之論文各一份
- □國際合作研究計畫國外研究報告書一份

執行單位：臺大醫院內科

中　華　民　國　91　年　10　月　29　日

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一、中文摘要

血中同胱氨酸濃度的增加最近被認為是心血管疾病(包括腦中風)的新興危險因子。先前的研究顯示高同胱氨酸血症會損害肱動脈血管功能，而降低同胱氨酸濃度則可改善其功能。高同胱氨酸血症亦已顯示會降低腦血管反應性(腦血管反應性降低會增加腦中風的機會)，但降低同胱氨酸濃度是否能改善腦血管反應性的功能則仍未確定。因此吾人對高血壓病人(腦中風之高危險群)進行葉酸治療以降低同胱氨酸濃度，結果顯示可改善高血壓病人的腦血管反應性。本實驗顯示降低同胱氨酸濃度或許對高血壓病人的腦中風預防有所助益。

關鍵詞：同胱氨酸、腦血管反應性

Abstract

Elevated plasma homocysteine levels have been recently implicated as a newly independent risk factor for cardiovascular disease, including stroke. Human studies have revealed that hyperhomocysteinemia could impair brachial vascular function, and reduction of homocysteine levels could improve vascular function. Meanwhile, hyperhomocysteinemia has also been shown to decrease cerebrovascular reactivity (CVR), impairment of which has been shown to indicate increased risk for ischemic stroke. However, whether homocysteine-lowering treatment could improve CVR remains undetermined. Therefore, we examined the homocysteine-lowering effect on the patients with hypertension, which is a major risk factor for stroke. Our result showed that homocysteine reduction could ameliorate CVR in hypertensive patients with relatively normal homocysteine levels at baseline. The result implicated that the homocysteine reduction in hypertensive patients would be beneficial in stroke.

Keywords: homocysteine, cerebrovascular reactivity

二、緣由與目的

Cerebrovscular reactivity (CVR) is an index of the vasoregulatory capacity of the cerebral vessels, which maintains constant flow in the face of wide fluctuations in perfusion pressure. Impaired CVR therefore may indicate increased risk for ischemic stroke. [1]

Hyperhomocysteinemia is an emerging risk factor for atherosclerosis and consequent ischemic stroke. [2] In humans, mild to moderate hperhomocysteinemia (15 to 30 μmol/L), either fasting or post-methionine load, has been associated with nitric oxide-mediated impairment of brachial artery vasodilation, [3] and vitamin treatment with folic acid has shown to improve vasodilation. [4] Meanwhile, such mild to moderate hyperhomocysteinemia has also been revealed to impair CVR. [5] However, whether homocysteine-lowering treatment could ameliorate CVR is not investigated. Previous meta-analysis showed a graded effect of homocysteine levels on the risk, similar to other risk factors. [2] Moreover, an elevated HCY level is found to dramatically increase the risk of major cardiovascular events, including stroke, in patients with hypertension. [6] The specific objective of this study was to investigate the effect of homocysteine reduction with folic acid on CVR in hypertensive patients.

Thirty subjects were included if they were previously diagnosed hypertensive

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Thirty subjects were included if they were previously diagnosed hypertensive (systolic blood pressure ≥ 140 mm Hg and diastolic blood pressure ≥ 90 mm Hg) and well controlled with antihypertensive agents. The subjects were randomly divided into 2 groups (15 subjects in each group). Group 1 took folic acid 5 mg (Johnson Chemical Pharmaceutical Works Ltd., Taiwan) per day for 3 months and group 2 was the control group without intake of folic acid. After an overnight fast (8 to 10 hours), venous blood samples were drawn from all subjects to measure the concentrations of homocysteine, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, glucose, folate, and vitamin B_{12}. Echocardiography was then performed. Laboratory evaluations and ultrasound assessments were performed at baseline and 3-month follow-up, respectively. Samples were placed into tubes containing EDTA and centrifuged within 30 minutes at 2000 rpm for 10 minutes, [7] then separated and stored at -70°C until analysis. Total homocysteine concentrations was measured by fluorescence polarization immunoassay (Abbott Imx System). Folate and vitamin B_{12} were determined by microparticle enzyme immunoassay (Abbott Ax SYM System). Transcranial Doppler ultrassonography (TCD) was used to evaluate transient hyperemic response in the middle cerebral artery (MCA) after breath holding for 30 seconds. Ultrasound measurements using a 2-4 MHz TCD probe (HP 5500, USA) was performed. [7] Systolic flow velocity (FVS) of the MCA was recorded at baseline, and after breath holding. Transient hyperemic response ratio (THRR) was obtained using the formula: $\text{THRR} = (\text{FVS}_{\text{hyperemia}} - \text{FVS}_{\text{basal}}) / \text{FVS}_{\text{basal}}$. Chi-square test was used to test the difference among the binary groups. Continuous data was expressed as mean ± SD value. For the continuous data, comparisons between two groups were analyzed by Student's *t* test. The changes of continuous data in the same group were compared by paired *t* test. $P<0.05$ was considered significant.

三、結果與討論

Homocysteine levels were significantly decreased after folic acid treatment in treatment group (10.2 ± 1.4 μmol/L versus 8.8 ± 1.2 μmol/L at baseline, $P<0.05$). THRR was also improved in treatment group (28.8 ± 6.3% versus 23.2 ± 5.2% at baseline, $P<0.05$). After folic acid treatment, significant correlation was found between the changes of homocysteine levels and CVR values ($r=-0.52$, $P<0.05$). To further investigate the relation between homocysteine levels and CVR after vitamin treatment, we arbitrarily divided the subjects of treatment group into 2 subgroups according to the homocysteine reduction greater than 1.0 μmol/L (median). Eight subjects with reduction greater than 1.0 μmol/L had significant CVR improvement. The other 7 subjects otherwise had no significant CVR change. In contrast, the change of folate concentrations did not correlate with the change of CVR significantly.

Till now, whether the improvement of vascular function is via homocysteine reduction or folate supplement is still in debate. [8] In our study, we first revealed that homocysteine reduction but not folate supplement per se improves CVR.

四、計畫成果自評

To our knowledge, this is the first study to demonstrate the effect of homocysteine reduction on CVR, which is an indicator of stroke. Furthermore, the improvement of CVR was found in patients with well-controlled hypertension. This implicates that homocysteine reduction is still beneficial in these patients. We hope that this study result would broaden the management profile in hypertension and stroke.

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