行政院國家科學委員會專題研究計畫　成果報告

N-methyl-D-aspartate 受體之調控與難治型精神分裂症—以 Glycine Transporter 為標的

計畫類別：個別型計畫
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一、中文摘要

近年來，N-methyl-D-aspartate (NMDA)受體的功能低下被認為是精神分裂症的可能成因。目前已有少數臨床研究探討將NMDA 促進劑作為輔助治療的效果，例如，D-serine (內生性 NMDA-glycine site 致效劑)、sarcosine (即 N-methylglycine，一種內生性 glycine transporter 抑制劑)，均顯示其能加強傳統及新一代抗精神病劑(除了clozapine 之外)對活性、負性症狀及認知功能障礙的療效，且相當安全。難治型精神分裂症(特別是對最後一線抗精神病劑clozapine療效不佳者)目前在臨床上仍相當棘手，過去發現補充 D-serine 或其他NMDA 致效劑對此類患者並無顯著效果。本研究進一步探討 sarcosine 輔助療法對難治型精神分裂症之效果及安全性。

我們已完成收案 40 位對於 clozapine療效不佳的精神分裂症患者，在 clozapine劑量不變的情況下，以雙盲方式隨機給予sarcosine (2000 mg/day)或安慰劑，為期六週。我們每兩週評估其療效、安全性、生活品質、glycine 與 sarcosine 等胺基酸血中濃度。

結果如同其他 NMDA 致效劑，glycine transporter 抑制劑(sarcosine)，並無助於難治型精神分裂症患者之活性、負性症狀改善和認知功能表現。血漿 clozapine 濃度未受 sarcosine 影響。

本研究結果預期可以發表於國外重要學術期刊。此外，我們以本計畫之經費支持，已有 6 篇文獻被接受發表，請參考 <**五、參考文獻**> 所列。

關鍵詞：N-methyl-D-aspartate 受體，glycine transporter，sarcosine，精神分裂症

Abstract

In recent one decade, hypofunction of N-methyl-D-aspartate (NMDA) receptor has been implicated in the pathophysiology of schizophrenia. Hence, enhancing NMDA neurotransmission was considered as a new approach for schizophrenia treatment. To date, there have been a few pilot studies exploring the efficacy of NMDA enhancers as adjuvant therapy for schizophrenia, for instance, D-serine (an endogenous agonist of the NMDA-glycine site) and sarcosine (N-methylglycine, an endogenous glycine transporter I inhibitor). They were not only well-tolerated but also synergistic in improving positive, negative and cognitive symptoms in those receiving typical and atypical antipsychotics (except clozapine).

Refractory schizophrenia (particularly clozapine-resistant) is still a difficult clinical issue at present. Previous studies revealed that add-on treatment of D-serine or other agonists of NMDA receptor failed to give significant benefits in such patients. The goal of this study is to investigate the efficacy and safety of sarcosine adjuvant therapy in refractory schizophrenia, and to identify the predictors for treatment response to NMDA enhancers.

This is a one-year proposal. Forty clozapine-resistant schizophrenic patients were enrolled in a 6-week randomized, double-blind, placebo-controlled trial of sarcosine (2000 mg/day), were added to their stable clozapine regimens. Measurements of clinical efficacy, side effects, quality of life, serum glycine and sarcosine levels were performed biweekly. At the beginning and end of the trial, we evaluate plasma levels of clozapine for confirmation of therapeutic concentration. The efficacy and safety of sarcosine were analyzed.

For these refractory schizophrenic patients, sarcosine produced no greater improvement when co-administered with clozapine than placebo plus clozapine at weeks 2, 4, and 6. Sarcosine was well tolerated and no significant side-effect was noted. Plasma clozapine levels were not be altered by sarcosine treatment.

The study results can be published in relevant outstanding journals. During this year of the study, we have published 6 papers (please see the ref).

Key words: Atypical antipsychotics, neurotransmitter, pharmacogenetics, schizophrenia

二、緣由與目的

精神分裂症的成因至今尚未明朗。近年來，N-methyl-D-aspartate (NMDA)受體的功能低下被認為是精神分裂症的可能成因，於是，促進 NMDA 受體的功能漸成為治療精神分裂症的新思維。目前已有少數

臨床研究探討將NMDA促進劑作為輔助治療的效果，例如，D-serine (內生性NMDA-glycine site致效劑)、sarcosine (即N-methylglycine，一種內生性 glycine transporter 抑制劑)，均顯示其能加強傳統及新一代抗精神病劑(除了 clozapine 之外)對活性、負性症狀及認知功能障礙的療效，且相當安全。

難治型精神分裂症(特別是對最後一線抗精神病劑 clozapine 療效不佳者)目前在臨床上仍相當棘手，過去發現補充 D-serine 或其他 NMDA 致效劑對此類患者並無顯著效果。最近，我們針對急性發作患者的研究則發現，sarcosine 明顯優於 D-serine，能更快速有效地改善活性及負性症狀。本研究目的即在探討 sarcosine 輔助療法對難治型精神分裂症之效果及安全性。

三、結果與討論

本案為 1 年期計畫，我們已完成收案 40 位對於 clozapine 療效不佳的精神分裂症患者，在 clozapine 劑量不變的情況下，以雙盲方式隨機給予 sarcosine (2000 mg/day) 或安慰劑，為期六週。我們每兩週評估其療效、安全性、生活品質、glycine 與 sarcosine 等胺基酸血中濃度。在研究開始及結束時，我們並測定血漿 clozapine (及其代謝物)濃度以確定其在治療濃度範圍內，及是否受到研究用藥的影響。

結果如同其他 NMDA 致效劑，glycine transporter 抑制劑(sarcosine)組（n = 20）與安慰劑組（n = 20）於各方面的臨床表現皆無顯著差異，也就是說 sarcosine 並無助於難治型精神分裂症患者之活性、負性症狀、與一般精神病理之改善。

Sarcosine 組則於活性症狀（Positive and Negative Syndrome Scale 之 Positive Subscale）之平均分數由 18.0 降至 17.7；安慰劑組則由 16.5 降至 15.8。Sarcosine 組於負性症狀（Positive and Negative Syndrome Scale 之 Negative Subscale）之平均分數由 27.0 降至 25.1；安慰劑組則由 26.6 降至 24.2。Sarcosine 組於一般精神病理（Positive and Negative Syndrome Scale 之 General Psychopathology）之平均分數由 35.1 降至 31.2；安慰劑組則由 33.7 降至 32.1，且這些差異皆具統計顯著意義。我們也分析兩組患者間於 Continuous performance test, Wisconsin Card Sorting Test, 以及 Tower of Hanoi 等認知功能的差異，結果兩組之間也未見明顯差異。兩組之間於副作用方面的表現也無顯著差別。血漿 clozapine 濃度未受 sarcosine 影響。

四、計畫成果自評

本案為 1 年期計畫，我們已完成收案 40 位對於 clozapine 療效不佳的精神分裂症患者。研究結果預期可以發表於國外重要學術期刊。此外，我們以本年度計畫之經

費支持，已有 6 篇 SCI 文獻被接受發表，請參考 **<五、參考文獻>** 所列。

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