# ニューロン・グリア間におけるD型セリンの分子機構解明

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N-Methyl-D-aspartate (NMDA)受容体を介するグルタミン酸神経伝達の異常は、統合失調症などの精神疾患の病態に関与していることが示唆されている。NMDA受容体のグリシン調節部位に作用するD型セリンは脳内に存在する酵素セリンラセマーゼ（SRR）によってL型セリンより合成されることが知られている。以前我々は、統合失調症の患者では、血液中D型セリン濃度が健常者と比較して有意に減少していることを報告し、統合失調症の病態におけるNMDA受容体機能低下仮説を支持する結果を報告した（Arch Gen Psychiatry 2003）。またカロリンスカ研究所との共同研究として、初発で未治療の統合失調症患者の脳脊髄液中の全セリン濃度に対するD型セリン濃度の割合が健常者と比較して有意に減少していること（Prog Neuropsychopharmacol Biol Psychiatry 2005）、およびグルタミン/グルタミン酸濃度比が健常者と比較して有意に増加していることを報告した（BMC Psychiatry 2005）。これらの結果は、統合失調症の発症時、脳ではD型セリンの合成・分解に係る過程やグリアーニューロン間におけるグルタミン/グルタミン酸サイクルが異常になっている可能性を示唆している。すなわち、統合失調症の病態にグリアの異常が関与している可能性を強く示唆している（Curr Psychiatry Rev 2005）。

次に、ヒトSRR遺伝子について統合失調症との関連研究を行なった。5′-RACE解析により、SRRには4種類の5′非翻訳エクソン（Exon 1a-1d）が存在することを明らかにし、それらエクソンの選択的使用によって4種類のmRNA（Isoforms a-d）が生成されることを見いだした。また脳においては、Isoform bが主である事が判った。これらゲノム情報に基づきSRR遺伝子の変異・多型検索を実施した結果、exon 1b近傍に2個のSNPとintron 5および3′非翻訳部位に1個ずつ頻度の低いSNPを見つけた。本研究では頻度の高い2個のSNP（exon 1b近傍の2個のSNP）について解析を行なった結果、両群で差はなかった（Biol Psychiatry 2005）。

一方、死後脳を用いた研究は、統合失調症などの精神疾患の病態研究に不可欠であるが、脳内のアミノ酸濃度は、死亡から脳摘出して凍結するまでの時間（PMI: postmortem interval）などによって大きく影響することが知られている。

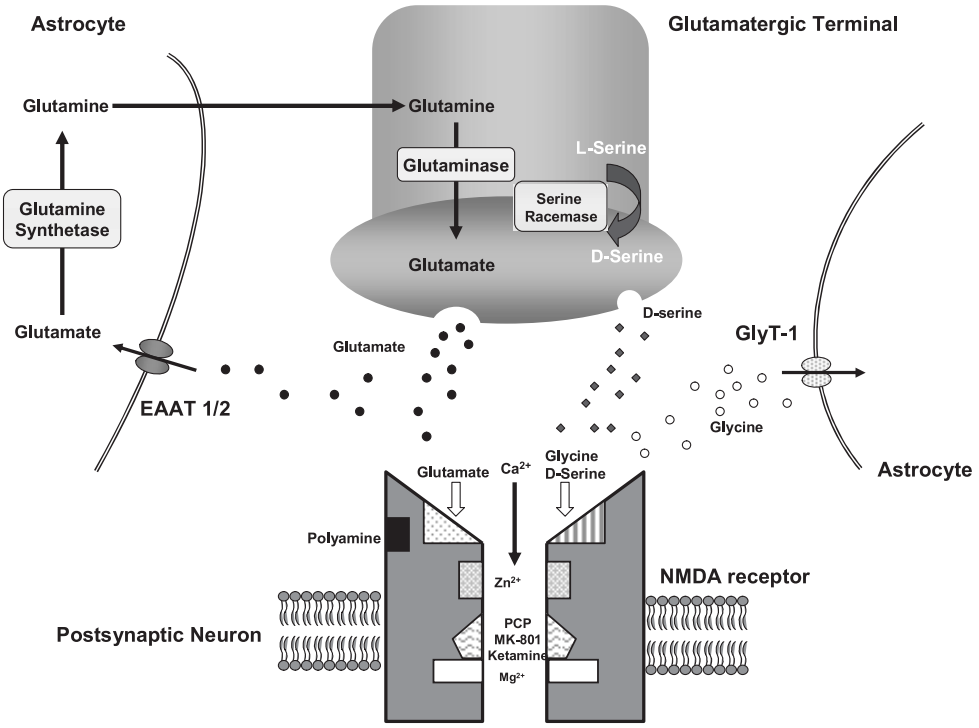


**図　統合失調症の病態におけるグリアーニューロン相互作用**

グリアーニューロン間におけるグルタミン-グルタミン酸サイクルによって生成されたグルタミン酸は後シナプスに存在するNMDA受容体に作用し、その後、グリア細胞に存在するグルタミン酸トランスポーター（EAAT 1/2）にて取り込まれる。またニューロンに存在するセリンラセマーゼによって生成されたD型セリンはグリシン同様、NMDA受容体のグリシン調節部位に作用する。グリシンはグリア細胞に存在するグリシン・トランスポーター（GlyT-1）によって取り込まれる。

今回、マウス脳を用いて脳内アミノ酸濃度とPMIとの関係を調べ、次にマウスで求めた補正式を米国スタンレイ財団より提供された死後脳（コントロール、統合失調症、双極性障害、うつ病各15例）に当てはめ、各サンプルの死亡時期におけるアミノ酸（グルタミン酸、グルタミン、グリシン、D型セリン、L型セリン）濃度を測定した。その結果、D型セリン、L型セリン、グルタミン、グリシンについては4群で有意な差は無かったが、グルタミン酸に関しては、双極性障害、うつ病群において高値を示した（Biol Psychiatry 2007）。近年、治療抵抗性のうつ病患者を対象とした臨床試験研究より、NMDA受容体拮抗薬ケタミンに即効性の抗うつ作用があることが報告されており、うつ病の病態にグルタミン酸が重要な役割を果たしている可能性が指摘されている。今回の私たちの研究成果は、このケタミンの臨床効果を支持する結果であると思われる。

統合失調症を対象とした臨床試験研究より、NMDA受容体のグリシン調節部位の内在性アゴニストであるグリシンやD型セリンに治療効果があることが報告されている。しかしながら、体内動態や脳移行性等の問題により、多量のグリシンやD型セリンを服用する必要がある。我々はNMDA受容体拮抗薬の投与で引き起こされる統合失調症のモデル動物（プレパルス抑制障害モデル）を用いて、選択的なD型アミノ酸酸化酵素（D型セリンを分解する酵素）阻害剤を併用することにより、D型セリンの投与量を大幅に軽減することを見出した。また、NMDA受容体近傍の細胞外グリシン濃度は、グリア細胞に存在するグリシン・トランスポーター（GlyT-1）によって制御されている。私たちは、NMDA受容体拮抗薬の投与で引き起こされる統合失調症のモデル動物（認知機能障害モデル）において、海馬におけるGlyT-1が増加しており、GlyT-1阻害薬が認知機能障害に有効であることを見出し、統合失調症の新規治療薬として有望であることを報告した（Eur Neuropsychopharmacol 2008）。またD型セリン合成酵素SRRと相互作用するPICK1遺伝子欠損マウスの発達期の脳では、全セリン濃度に対するD型セリンの割合が有意に減少していることを見出し、PICK1遺伝子が脳内D型セリン合成に関わっていることを報告した（Biol Psychiatry 2007）。さらに、ヒトPICK1遺伝子多型が覚せい剤精神病の発症に関わっていることを報告した（Am J Psychiatry 2007）。

以上の結果より、D型セリンおよびグリシンはNMDA受容体の内在性調節因子として、統合失調症などの精神疾患の病態に関与している可能性があり、グリア細胞は精神神経疾患の新しい治療ターゲットとして期待されている。

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