非定型抗精神病薬リスペリドンに結合したD2ドーパミン受容体の構造

ドーパミンはやる気に関わる神経伝達物質として有名ですが、統合失調症、パーキンソン病、うつ病、注意欠如・多動性障害や悪心・嘔吐などの疾患の原因にもドーパミンの需要が関わっていることが報告されています。実際にこの論文でD2ドーパミン受容体（DRD2）と結合しているリスペリドンは非定型抗精神病薬（非定型抗精神病薬は定型抗精神病薬の後から開発されて、受容体からの解離が早く、副作用が少ないなどの特徴を持ちます）として市販されています。構造情報からより良い薬をデザインする際の参考になると思い紹介させていただきます。

紹介論文

Structure of the D2 dopamine receptor bound to the atypical antipsychotic drug risperidone

Sheng Wang[1], Tao Che[1], Anat Levit[2], Brian K. Shoichet[2], Daniel Wacker[1] & Bryan L. Roth[1,3,4]

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[1]Department of Pharmacology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-7365, USA.

[2]Department of Pharmaceutical Chemistry, University of California San Francisco, San Francisco, California 94158-2280, USA.

[3]Division of Chemical Biology & Medicinal Chemistry, Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-7360, USA.

[4]National Institute of Mental Health Psychoactive Drug Screening Program (NIMH PDSP), School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-7365, USA.

要旨

Dopamine is a neurotransmitter that has been implicated in processes as diverse as reward, addiction, control of coordinated movement, metabolism and hormonal secretion. Correspondingly, dysregulation of the dopaminergic system has been implicated in diseases such as schizophrenia, Parkinson's disease, depression, attention deficit hyperactivity disorder, and nausea and vomiting. The actions of dopamine are mediated by a family of five G-protein-coupled receptors. The D2 dopamine receptor (DRD2) is the primary target for both typical and atypical antipsychotic drugs, and for drugs used to treat Parkinson's disease. Unfortunately, many drugs that target DRD2 cause serious and potentially life-threatening side effects due to promiscuous activities against related receptors. Accordingly, a molecular understanding of the structure and function of DRD2 could provide a template for the design of safer and more effective medications. Here we report the crystal structure of DRD2 in complex with the widely prescribed atypical antipsychotic drug risperidone. The DRD2–risperidone structure reveals an unexpected mode of antipsychotic drug binding to dopamine receptors, and highlights structural determinants that are essential for the actions of risperidone and related drugs at DRD2.