Journal Club No.843 Nov.12 2019

古谷　章悟

Cryo-EM を使ったヒト α1β3γ2GABA$_A$ 受容体の構造の解析

脳での速い抑制性神経伝達は、主に神経伝達物質の γ-アミノ酪酸（GABA）とシナプスでのその標的である A 型 GABA 受容体（GABA$_A$ 受容体）によって仲介される。この受容体の機能が障害されると、てんかんや不安障害、不眠症などの神経疾患や精神障害が発症する。また、GABA$_A$ 受容体は、ベンゾジアゼピン系薬やバルビツール酸系薬、麻酔薬やエタノールなどの多様な治療薬の標的でもある。しかし、GABA$_A$ 受容体のどこに作用するかわからないまま開発されてきた。本論文では、クライオ電子顕微鏡を用いて、GABA$_A$ 受容体の構造と数種の薬剤との複合体の構造を解いた。クライオ電子顕微鏡が創薬開発の技術基盤として有効であることを示し、とても興味深かったため紹介する。

紹介論文

GABA$_A$ receptor signalling mechanisms revealed by structural pharmacology

Simonas Masiulis[1*], Rooma Desai[2], Tomasz Uchański[3,4], Itziar Serna Martin[5], Duncan Laverty[1], Dimple Karia[5], Tomas Malinauskas[5], Jasenko Zivanov[1], Els Pardon[3,4], Abhay Kotecha[6], Jan Steyaert[3,4], Keith W. Miller[2 *] & A. Radu Aricescu[1,5*]

([1]MRC Laboratory of Molecular Biology, Cambridge Biomedical Campus, Cambridge, UK. [2]Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA. [3]Structural Biology Brussels, Vrije Universiteit Brussel (VUB), Brussels, Belgium. [4]VIB-VUB Center for Structural Biology, VIB, Brussels, Belgium. [5]Division of Structural Biology, Wellcome Centre for Human Genetics, University of Oxford, Oxford, UK. [6]Materials and Structural Analysis, Thermo Fisher Scientific, Eindhoven, The Netherlands.)

Nature 565, 454–459 *(2019)*

要旨

Type-A γ-aminobutyric (GABA$_A$) receptors are ligand-gated chloride channels with a very rich pharmacology. Some of their modulators, including benzodiazepines and general anesthetics, are among the most successful drugs in clinical use and are common substances of abuse. Without reliable structural data, the mechanistic basis for the pharmacological modulation of GABA$_A$ receptors remains largely unknown. Here we report several high-resolution cryo-electron microscopy structures in which the full-length human α1β3γ2L GABA$_A$ receptor in lipid nanodiscs is bound to the channel-blocker picrotoxin, the competitive antagonist bicuculline, the agonist GABA (γ-aminobutyric acid), and the classical benzodiazepines alprazolam and diazepam. We describe the binding modes and mechanistic effects of these ligands, the closed and desensitized states of the GABA$_A$ receptor gating cycle, and the basis for allosteric coupling between the extracellular, agonist-binding region and the transmembrane, pore-forming region. This work provides a structural framework in which to integrate previous physiology and pharmacology research and a rational basis for the development of GABA$_A$ receptor modulators.