Resolvins as novel targets for rapid-acting antidepressants

Satoshi Deyama

Lab. Mol. Pharmacol., Inst. Med., Pharmaceut., Health Sci., Kanazawa Univ.

Major depressive disorder is one of the most widespread mental illnesses, affecting more than 264 million people worldwide (World Health Organization, 2019) and causing enormous personal and socioeconomic burden. Conventional monoaminergic antidepressants have significant limitations, including delayed onset of therapeutic response and low efficacy: approximately one-third of depressed patients fail to respond to multiple antidepressant treatments and are considered treatment-resistant depression. Recent studies reveal that ketamine, an *N*-methyl-D-aspartate receptor antagonist, produces rapid antidepressant actions in patients with treatment-resistant depression. However, clinical use of ketamine as an antidepressant is limited due to its serious drawbacks including psychotomimetic/dissociative effects and abuse potential. Thus, there is a continuing unmet need for the development of safer rapid-acting antidepressants. I have demonstrated that resolvins, bioactive metabolites derived from docosahexaenoic acid and eicosapentaenoic acid, produce antidepressant effects through mechanisms (activation of mTORC1 signaling) similar to those underlying the rapid antidepressant effects of ketamine. Taken together, resolvins could be promising targets for the development of novel rapid-acting antidepressants with fewer side effects than ketamine, since resolvins are endogenous lipid mediators that play an important role in homeostasis.

うつ病は、患者個人のみならず社会経済に与える損失が大きい身近な精神疾患であり、全世界のうつ病患者数は2億6400万人以上と推計されている(WHO, 2019年)。モノアミン神経系に作用する既存の抗うつ薬は、効果発現までに数週間以上を要し、約3割の患者には無効である(治療抵抗性うつ病)。一方、近年の研究により、NMDA受容体拮抗薬ケタミンが、治療抵抗性うつ病患者に即効性の抗うつ作用を示すことが明らかにされているが、依存性や統合失調症様症状の惹起などの重大な副作用のため、ケタミン自体の抗うつ薬としての使用には大きな制約がある。そのため、ケタミンより副作用の少ない新たな即効性抗うつ薬の開発が求められている。私は、ドコサヘキサエン酸およびエイコサペンタエン酸の活性代謝物レゾルビン類に着目し、レゾルビン類がケタミンと類似のメカニズム(mTORC1経路活性化)で抗うつ作用を示すことを発見した。レゾルビン類は、恒常性維持に関与する内因性脂質メディエーターであることから、ケタミンより安全性面で優れた新たな即効性抗うつ薬の創薬標的になると期待できる。