第539回 難研セミナー

第112回 難治疾患共同研究拠点セミナー

下記により難研セミナーを開催しますので、多数御来聴下さい。

日時：平成27年10月23日（金）17:00～18:00
場所：M&Dタワー9階 大学院講義室4

演者：Professor Ulrik Gether (University of Copenhagen)
演題：The dopamine transporter: a key player in psychostimulant addiction and dopaminergic pathologies

要旨：

Cocaine and amphetamine exert their action via binding to the presynaptic dopamine transporter (DAT) that mediates rapid reuptake of dopamine from the synaptic cleft. We wish to gain insight into the molecular mechanisms underlying drug action at DAT, to reveal mechanisms governing the activity and availability of DAT in the synaptic terminals and to understand how alterations in these processes contribute to psychostimulant addiction and neuropsychiatric diseases. By characterizing the molecular basis for the interaction of cocaine with DAT, as well as of atypical inhibitors (e.g. benzotropines), we have evidence for a model in which the conformation of the transporter affects the stimulatory effect of the inhibitor. This has led the idea of using atypical DAT inhibitors in addiction treatment. In contrast to cocaine, amphetamine is a DAT substrate and promotes reverse transport of dopamine via DAT. We have shown that this requires interaction of Ca²⁺/Calmodulin dependent kinase IIα (CaMKIIα) with the C-terminus of the transporter. Our recent work demonstrate that membrane-permeable C-terminal DAT peptides corresponding to the CaMKIIα binding domain not only inhibit amphetamine-induced dopamine release in the striatum but also attenuate amphetamine-induced hyperlocomotion in mice. The data suggest that by targeting DAT protein-proteins it might be possible to blunt amphetamine action, thereby opening up for yet another principle in addiction treatment. Finally, our recent work has shown how inherited and de novo mutations in DAT can contribute to dopaminergic pathologies. We have identified patients with DAT missense mutations suffering both from neuropsychiatric disease and early-onset parkinsonism. The mutations elicit distinct changes in transporter function reflecting the disease phenotypes of the patients. The results should prove highly important for further dissecting the relationship between dopaminergic dysfunction, addiction and neuropsychiatric disorders.

連絡先：分子神経科学分野・田中光一（内線：5846）
共催：神経病理学分野・岡澤均（内線：5847）