＜セミナー開催のお知らせ･Seminar Announcement＞

農学部・神経科学セミナー（第 10 回）

本セミナーは不定期に海外からの研究者をお招きして開催しております。
今回は、神経科学の基礎及びその臨床応用を研究する世界的なトップランナーの研究者 2 名が来日されますので、セミナーを企画しました。お時間の許す限りご参加下さい。

日時：2025 年 5 月 8 日（木）15：00～17：00
場所：東京大学農学部 2 号館 1 階　化学第 2 講義室
Date: 15:00-17:00, May 8, 2025
Venue: Faculty of Agriculture Building No.2
- Chemical Lecture Room 2 (first floor)

Program

15:00-16:00
Mazen Kheirbek (University of California San Francisco)
Title: Understanding the neural code of stress to control anhedonia

16:00-17:00
Anatol Kreitzer (MapLight Therapeutics)
Title: Development of Muscarinic Agonists as a Novel Class of Antipsychotics

次ページに abstract, reference が掲載されています。

（＊事前のお申込みは不要です）

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Understanding the neural code of stress to control anhedonia

Mazen Kheirbek

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Abstract: Anhedonia, the diminished drive to seek, value, and learn about rewards, is a core feature of major depressive disorder. The neural underpinnings of anhedonia and how this emotional state drives behavior remain unclear. Here we investigated the neural code of anhedonia by taking advantage of the fact that when mice are exposed to traumatic social stress, susceptible animals become socially withdrawn and anhedonic, whereas others remain resilient. By performing high-density electrophysiology to record neural activity patterns in the basolateral amygdala (BLA) and ventral CA1 (vCA1), we identified neural signatures of susceptibility and resilience. When mice actively sought rewards, BLA activity in resilient mice showed robust discrimination between reward choices. By contrast, susceptible mice exhibited a rumination-like signature, in which BLA neurons encoded the intention to switch or stay on a previously chosen reward. Manipulation of vCA1 inputs to the BLA in susceptible mice rescued dysfunctional neural dynamics, amplified dynamics associated with resilience, and reversed anhedonic behaviour. Finally, when animals were at rest, the spontaneous BLA activity of susceptible mice showed a greater number of distinct neural population states. This spontaneous activity allowed us to decode group identity and to infer whether a mouse had a history of stress better than behavioural outcomes alone. This work reveals population-level neural dynamics that explain individual differences in responses to traumatic stress, and suggests that modulating vCA1–BLA inputs can enhance resilience by regulating these dynamics.

Reference:

Xia F, Fascianelli V, Vishwakarma N, Ghinger FG, Lalani L, Gergues M, Fusi S, Kheirbek MA. Understanding the neural code of stress to control anhedonia. *Nature*. 637, 654–662 (2025). PMID: 39633053, PMCID: PMC11735319

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Gergues MM, Han KJ, Choi HS ,Brown B, Clausing KJ, Turner VS, Vainchtein ID, Molofsky AV, Kheirbek MA. Circuit and molecular architecture of a ventral hippocampal network. *Nature*

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Danielson NB, Kaifosh P, Zaremba JD, Lovett-Barron M, Tsai J, Denny CA, Balough EM, Goldberg AR, Drew LJ, Hen R, Losonczy A, Kheirbek MA. Distinct Contribution of Adult-Born Hippocampal Granule Cells to Context Encoding. *Neuron*. 2016 Apr 6;90(1):101-12.

Development of Muscarinic Agonists as a Novel Class of Antipsychotics

Anatol Kreitzer

MapLight Therapeutics

Abstract: Muscarinic agonists represent a new class of treatments for psychosis with a mechanism distinct from typical and atypical antipsychotics. The muscarinic subtype M4 has been proposed as the primary mediator of efficacy but results from recent clinical trials with M4-selective compounds have drawn this hypothesis into question. Instead, activation of both M1 and M4 receptor subtypes may be required for robust treatment effects. We characterized the clinical-stage muscarinic agonist ML-007 and explore its therapeutic potential for treating psychosis in schizophrenia and Alzheimer's disease. ML-007 is a potent brain-penetrant agonist at both M1 and M4 muscarinic receptors that has demonstrated strong efficacy across a range of preclinical models of psychosis in schizophrenia including amphetamine-induced hyperlocomotion, PCP-induced hyperlocomotion, and conditioned avoidance response. Moreover, ML-007 is approximately ten-fold more potent than the comparator xanomeline in all animal models. Dose-response experiments in M1 and M4 knockout mice reveal that the efficacy of ML-007 is dependent on both M1 and M4 receptors. Taken together, our data--along with recent clinical trial outcomes--suggest that activation of both M1 and M4 receptors contribute to the potent efficacy of muscarinic agonists in treating psychosis.

Reference:

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Paul SM, Yohn SE, Brannan SK, Neugebauer NM, Breier A. Muscarinic Receptor Activators as Novel Treatments for Schizophrenia. Biol Psychiatry. 2024 Oct 15;96(8):627-637. doi: 10.1016/j.biopsych.2024.03.014. Epub 2024 Mar 25. PMID: 38537670.

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