DEPARTMENT
OF PHARMACEUTICAL SCIENCES

# Seminars on Drug Sciences (SDS)

Lecture of


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# Prefrontal astrocyte-derived kynurenic acid disrupts cognitive functions


Astrocyte dysfunction is increasingly recognized as a key contributor to circuit-level abnormalities in psychiatric disorders, yet the mechanisms linking altered glial activity to cognitive impairment remain insufficiently understood. Here, we investigate how astrocyte activity in the prefrontal cortex shapes neuronal function, metabolism, and behavior. Using chemogenetic approaches in mice, we selectively manipulated astrocyte activity and examined downstream effects on the kynurenine (KYN) pathway, neuronal circuit dynamics, and cognition. To establish causality, we combined pharmacological rescue strategies with astrocyte-specific knockdown of kynurenine aminotransferase II (KAT II), the enzyme responsible for converting KYN into kynurenic acid (KYNA). We further assessed astrocyte function and KYN pathway alterations in a maternal immune activation (MIA) model of neuropsychiatric risk.

We found that astrocyte activation increases KYNA levels, a neuroactive metabolite that antagonizes NMDA receptors. Elevated astrocyte-derived KYNA disrupts prefrontal circuit function by suppressing parvalbumin-positive interneuron activity, leading to increased activity of pyramidal neurons. This imbalance results in deficits across multiple cognitive domains, including working memory, temporal order memory, and sensorimotor gating. Importantly, reducing KYNA synthesis mitigates these impairments. In the MIA model, increased astrocyte reactivity and KYNA levels were similarly associated with deficits in episodic-like memory.

Together, these findings identify a mechanistic astrocyte-KYNA-interneuron axis that regulates cortical excitability and cognitive performance. They highlight dysregulated glial metabolism as a convergent pathway underlying cognitive dysfunction across both environmental and cell-specific perturbations, providing a conceptual framework for understanding astrocyte contributions to psychiatric disease.


**Wednesday, April 8, 2026**
17:15 - 18:15
Lecture Hall 1, Pharmacenter, Klingelbergstrasse, 50, Basel

Host: Prof. L. Simmler
Neuropharmakology

University of Basel