Dottorato di Ricerca in Neuroscienze

*Università degli Studi di Torino*

# Seminars *in* Neuroscience

*2019 - 2020*


## Prof. Stefano Vicini

*Department of Pharmacology and Physiology*
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Title: Electroconvulsive Shock Enhances Responsive Motility and Purinergic Currents in hippocampal Microglia


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*Istituto di Neuroscienze-CNR*
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Title: The role of astrocyte calcium microdomains in prolonged LTP maintenance in the perirhinal cortex

## *December 12, 2019 @ 4 pm*

*Dipartimento di Scienze della Vita e Biologia dei Sistemi*
*Via Accademia Albertina 13 - Aula C*

DBios

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Neuroscience Institute Cavalieri Ottolenghi

**Host: Serena Bovetti & Alessandra Fiorio Pla**

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## Electroconvulsive Shock Enhances Responsive Motility and Purinergic Currents in hippocampal Microglia

Microglia are in a privileged position to both affect and be affected by neuroinflammation, neuronal activity and injury, which are all hallmarks of seizures and the epilepsies. Hippocampal microglia become activated after prolonged, damaging seizures known as status epilepticus (SE). However, since SE causes both hyperactivity and injury of neurons, the mechanisms triggering this activation remain unclear, as does the relevance of the microglial activation to the ensuing epileptogenic processes. In this study, we use electroconvulsive shock (ECS) to study the effect of neuronal hyperactivity without neuronal degeneration on mouse hippocampal microglia. Unlike SE, ECS did not alter hippocampal CA1 microglial density, morphology, or baseline motility. In contrast, both ECS and SE produced a similar increase in ATP-directed microglial process motility in acute slices, and similarly upregulated expression of the chemokine C-C motif chemokine ligand 2 (CCL2). Whole-cell patch-clamp recordings of hippocampal CA1sr microglia showed that ECS enhanced purinergic currents mediated by P2X7 receptors in the absence of changes in passive properties or voltage-gated currents, or changes in receptor expression. This differs from previously described alterations in intrinsic characteristics which coincided with enhanced purinergic currents following SE. These ECS-induced effects point to a "seizure signature" in hippocampal microglia characterized by altered purinergic signaling. These data demonstrate that ictal activity per se can drive alterations in microglial physiology without neuronal injury. These physiological changes, which up until now have been associated with prolonged and damaging seizures, are of added interest as they may be relevant to electroconvulsive therapy (ECT), which remains a gold-standard treatment for depression.

## The role of astrocyte calcium microdomains in prolonged LTP maintenance in the perirhinal cortex

Intracellular Ca$^{2+}$ transients in astrocytes play a key role in the modulation of synaptic transmission and plasticity in brain circuits. Until recently Ca$^{2+}$ signaling in fine processes was hampered by technical limitations. With the advent of genetically encoded calcium indicators and multi-photon laser scanning microscopy, it is now possible to study the Ca$^{2+}$ microdomains in astrocytic thin processes. Of note, genetic tools to selectively reduce astrocyte Ca$^{2+}$ signals in vivo are also available nowadays. We took advantage of these tools to study the role of astrocytic Ca$^{2+}$ dynamics on TBS induced prolonged LTP maintenance mediated by glial BDNF recycling. Since the release of astrocyte recycled BDNF must occur in a restricted time window of 10 minutes after LTP induction to allow LTP maintenance we here studied Ca$^{2+}$ signals before, during and soon after LTP induction with TBS. We used 2P-laser microscopy in layer II/III astrocytes of perirhinal cortex in slices from tamoxifen-inducible conditional p75$^{lox/lox}$-GLAST-CreER$^{T2}$-R26R mutant mice (p75-flox mice), in which glial cells are incapable of proBDNF recycling, and littermate controls. We found that in basal conditions Ca$^{2+}$ events were restricted to micrdomains in thin processes. TBS afferent stimulation for LTP induction induced transient, large, TTX-sensitive Ca$^{2+}$ events that involved all astrocytic compartments. Soon after the TBS, and during the critical window of 10 min after TBS, astrocytes recovered their basal Ca$^{2+}$ activity in microdomains. Both the frequency and the amplitude of spontaneous Ca$^{2+}$ transients were similar in control and p75-flox mice. To selectively inhibit astrocyte Ca$^{2+}$ transients, we used novel genetic tools such as the IP3-sponge p130PH and the calcium extruding human plasma membrane Ca$^{2+}$ pump (hPMCa). Following p130PH or hPMCA expression we found that both Ca$^{2+}$ transients and the long-lasting LTP were reduced. In conclusion our data reveal that astrocyte Ca$^{2+}$ microdomains in thin processes play a crucial role for LTP maintenance, unveiling a novel function of this form of Ca$^{2+}$ activity for brain function.

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