ASTROCYTE-MEDIATED SHORT-TERM SYNAPTIC DEPRESSION

Akademisk avhandling
Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin vid Göteborgs universitet kommer att offentligen försvaras i hörsal Ivan Östholm, Medicinaregatan 13, Göteborg, torsdagen den 17 september 2009 kl. 13.00

av
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Avhandllingen baseras på följande delarbeten:

I. My Andersson and Eric Hanse. Astrocytes impose post burst depression of release probability at hippocampal glutamate synapses. *Manuscript*.

II. My Andersson, Fredrik Blomstrand and Eric Hanse. Astrocytes play a critical role in transient heterosynaptic depression in the rat hippocampal CA1 region. *Journal of Physiology*. (2007) 585;843-852

III. My Andersson and Eric Hanse. Astrocyte-mediated short-term synaptic depression in the rat hippocampal CA1 area: two modes of decreasing release probability. *Manuscript*.

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Abstract
Short-term synaptic plasticity, the activity-dependent regulation of synaptic efficacy that occurs in the timeframe of milliseconds to seconds, is a fundamental property of the synapse, mostly attributed to changes in release probability. These changes are commonly ascribed to intrinsic mechanisms in the presynaptic terminal and to different transmitters acting on the presynaptic terminal. Astrocytes are the most abundant cell type in the brain. It has become increasingly clear that they can have a more active role in regulating neuronal signalling than their first established role of providing neuronal support. Astrocytes send out processes, which enwrap the synapses, in an ideal position to respond to synaptic transmission and in turn modulate synaptic function, such as short-term plasticity. However, not much is known about how astrocytes affect short-term synaptic plasticity.

The overall objective of this thesis was to examine the possible involvement of astrocyte-synapse signalling in short-term synaptic plasticity in the hippocampus. We used the acute rat hippocampal slice preparation and recorded the transmission at the glutamatergic CA3-CA1 synapses using extracellular and whole-cell patch-clamp recordings.

Hippocampal CA3-CA1 synapses as a population exhibit facilitation or augmentation milliseconds and seconds after a brief synaptic burst. However, we found that in the intermediate timeframe, between a couple of hundred milliseconds to seconds, these synapses exhibit a postburst depression (PBD). This PBD was found to be expressed as a reduction of release probability. The PBD displayed a cooperativity threshold as it was necessary to activate a critical number of synapses in order to elicit the depression. We found that the PBD develops over the first three postnatal weeks and that it is blocked when astrocyte metabolism is compromised. The PBD was blocked when a calcium chelator was delivered into the astrocytic network through a patch pipette, showing a requirement for astrocytic signalling.

Activation leading to PBD homosynaptically, also gave rise to a decrease in release probability in neighbouring inactive synapses, a transient heterosynaptic depression (tHeSD). The tHeSD developed over the same period as the PBD and was blocked by a blocker of astrocyte metabolism. In addition, the tHeSD was blocked by application of gap junction blockers. The tHeSD relied on $GABA_B$ and mGlu II/III receptors, but not on NMDA, adenosine A1 or mGlu I receptors.

Analysis of paired-pulse plasticity and relative vesicle pool size suggest that the tHeSD is expressed as a depression of resting vesicular release probability, causing a large increase of the paired-pulse ratio. In addition, the PBD was suggested to be a combination of vesicle depletion and augmentation, causing no change and a large decrease in paired-pulse ratio, respectively.

Hippocampal pyramidal neurons typically fire action potentials in short bursts in the behaving animal, at frequencies suitable for eliciting the PBD and the tHeSD. This suggests that astrocytes are critically involved in mediating a negative feedback synaptic transmission after a burst of synaptic activity.

Keywords: Glutamate, glia, hippocampus, plasticity, synapse

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