

# CALCIUM SIGNALLING IN ASTROCYTES AND MODULATION OF NEURAL ACTIVITY

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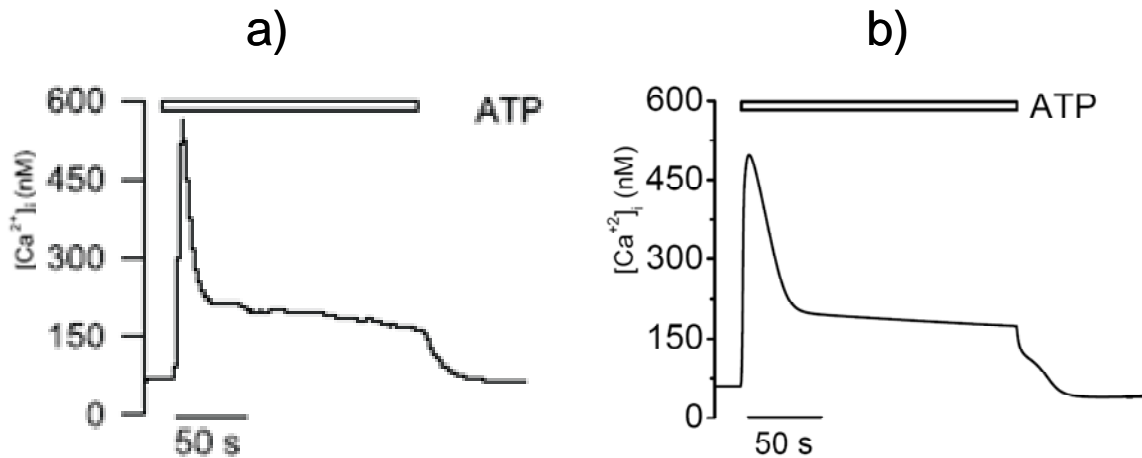
## ABSTRACT

Up to few years ago astrocytes have been considered as passive elements of brain, providing structural and metabolic support to the neurons, but playing little role in information processing. However, astrocytes express a wide variety of neurotransmitter receptors and recent researches revealed that astrocytes located near synapses respond to neurotransmitters (including glutamate, GABA, ATP etc.) with the elevation of their internal calcium levels [1-6]. The increase of the calcium level in these cells then mediates the release of glutamate and other neuroactive substances (feedback mechanism) capable to modulate the synaptic communication between neurons [7]. In particular, a relevant process is the release from astrocytes of ATP and glutamate. ATP is an important neurotransmitter and in turn its action on astrocytes is mediated by ionotropic (P2X) and metabotropic (P2Y) purinoreceptors [7, 8]; there is evidence that the release of ATP at the presynaptic site contributes to synaptic transmission between neurons by activating postsynaptic P2X receptors [8-10]. Glutamate is recognized to be one of the most important excitatory neurotransmitters in the brain. As for ATP, the elevation of the internal calcium level in astrocytes leads to the release of glutamate that modulates the activity of nearby neurons [7, 11]. In addition, a calcium independent pathway of glutamate release from astrocytes, through the activation of the P2X7 receptor, also occurs [7, 12]

In this contribution some of the above phenomena will be investigated both experimentally and by using a biophysical modeling approach. The experiments were performed on cultures of cortical astrocytes, and their main goal was that of characterizing their calcium signaling response in the presence of well defined extracellular ATP concentrations. By starting from the experimental results, a biophysical model describing the calcium dynamics in these cells was then built and the corresponding simulation results were compared with the experimental ones. In good agreement with the experimental findings, it was found that both the ionotropic and metabotropic ATP receptors play a key role in shaping the response of the astrocyte to ATP stimulation. Figure 1 shows the Ca-response of the astrocyte when a well defined external concentration of ATP is applied ( $[ATP]=3\mu M$ ). The response is biphasic and consists of a large initial peak followed by a sustained phase with smaller amplitude (plateau). For both panels the initial peak represents the effect of the release of calcium from the endoplasmic reticulum mediated by the metabotropic ATP receptor (through the production of  $IP_3$ ), while the plateau phase is mediated by the influx of calcium through (P2X7 receptors) the plasma membrane. This behaviour is critically dependent on the duration of ATP application: in fact if the stimulation time is shorter ( $\sim 20$  sec) the peak is still present, but the plateau disappears (data not shown).

Finally, to investigate the reciprocal modulation effects between astrocyte and neuron a biophysical model of this biological system was built. Then their reciprocal influences (electrophysiological point of view) were studied as a function of the system parameters.

**Keywords:** neuron, astrocyte, intracellular calcium, synapse, neural activity.



**Figure 1.** Panel a): experimentally recorded astrocyte response to ATP administration; panel b): response of the biophysical model.

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