The Model of Glutamate-induced Intracellular Ca^{2+} oscillation and Intercellular Ca^{2+} wave in brain astrocytes.

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Astrocyte, a kind of the glial cells, has glutamate receptors as well as neurons and it interacts with neurons in brain. In the cultured hippocampal astrocytes, they have spontaneous oscillation of intracellular Ca^{2+} concentration ($[Ca^{2+}]i$). The application of glutamate induces the several patterns of $[Ca^{2+}]i$ responses in the astrocytes. There are four patterns of the responses. They are a sustained oscillation, a damped oscillation, a step rise response and the sustained oscillation whose frequency gradually decreases. Glutamate can induce not only $[Ca^{2+}]i$ responses in an astrocyte, but also induce the propagation of Ca^{2+} wave among the astrocytes (Cornell-Bell et al, 1990). It is also found that metabotropic glutamate receptors (mGLuR) relate to the phenomena. The stimulated mGluR activates phospholipaseC (PLC) β through the activation of G-protein. The activated PLC β produces inositol1,4,5-triphosphate (IP_3) which binds to IP_3 receptor of the endoplasmic reticulum(ER) Ca^{2+} store and releases Ca^{2+} from the ER.

In the present study, astrocytic $[Ca^{2+}]i$ was calculated using the modified model of De Young and Keizer's model (1992). The modified model could produce not only the several patterns of the glutamate-induced $[Ca^{2+}]i$ responses but also spontaneous $[Ca^{2+}]i$ oscillation in a cell and Ca^{2+} wave through the cells. We at first tried to use the original De-Young and Keizer's $[Ca^{2+}]i$ model (1992). It models the detailed dynamics of IP_3 receptor/ Ca^{2+} channels (IP_3R), $[Ca^{2+}]i$ and the intracellular IP_3 concentration($[IP_3]$). While the model could produce a sustained $[Ca^{2+}]i$ oscillation, a damped oscillation and step rise $[Ca^{2+}]i$ response induced by the application of glutamate, the model could not produce the spontaneous $[Ca^{2+}]i$ oscillation nor induce Ca^{2+} wave. Hence we added the term of $[Ca^{2+}]i$ activated PLC δ to the model. PLC δ is preferentially expressed in astrocytes within CNS (Rebecchi and Pentyala, 2000) and it is proposed to relate to Ca^{2+} wave in astrocytes (Hoefer et al., 2002). Our new model could not only produce the glutamate-induced $[Ca^{2+}]i$ responses, which De-Young and Keizer's model could produce, but also produce the spontaneous $[Ca^{2+}]i$ oscillation and Ca^{2+} wave. Both De-Young and Keizer's model and our model could not produce the glutamate-induced sustained oscillation whose frequency gradually decreases.

According to our model, when the concentration of PLC δ ([PLC δ]) was low, $[Ca^{2+}]i$ doesn't oscillate. $[Ca^{2+}]i$ appears to oscillate spontaneously at higher [PLC δ]. The model has two production processes of IP_3. One is through PLC β and the other is through PLC δ. Ca^{2+}, which is released from IP_3–stimulated ER, activates PLC δ and PLC δ produces IP_3. The IP_3 again stimulates ER. Thus the IP_3 production process through PLC δ is regenerative, in other words, positive feedback process. Therefore, at high [PLC δ] in a astrocytes, the feedback process of IP_3 is active and the cell would have a spontaneous $[Ca^{2+}]i$ oscillation.

There are some differences between glutamate-induced sustained $[Ca^{2+}]i$ oscillation (GSCO) at low [PLC δ] and spontaneous $[Ca^{2+}]i$ oscillation (SCO) a high [PLC δ]. GSCO had a shorter period than SCO. The waveform of GSCO was like a sine wave, while that of SCO was like a relaxation oscillation. In our model, when an astrocyte was pair-pulse stimulated with IP_3, the second $[Ca^{2+}]i$ response was more suppressed than the first response. The suppression was recovered with longer inter pulse interval. IP_3-induced Ca^{2+} response in an astrocyte can have the refractory period. The suppression was more significant at the higher [PLC δ] and then the refractory period was longer than that at lower [PLC δ]. Therefore it is suggested that due to the longer refractory period, SCO at high [PLC δ] has a longer period and the waveform is the relaxation-type oscillation.

When the astrocytes had the higher [PLC δ], it had the SCO. At the proper range of [PLC δ], the interesting phenomena were observed. According to the bifurcation theory, it is called a sub critical bifurcation. When at the down phase, SCO was stimulated with IP_3, SCO ceased. SCO was recovered with the stimulation of IP_3 again. The phenomena have not yet been observed in an experiment and we hope some experimentalists to find it using the method of caged IP_3 substances.

The propagation of Ca^{2+} wave through the astrocytes is necessary to have the regenerative process of IP_3 by PLC δ. The velocity of the wave is around eight micro meter/ sec in our model and the speed is in the same range as that in experimental data (Cornell-Bell et al, 1990). As described previously, at higher [PLC δ], the asctrocytes had SCO. They were arranged to line in one-dimension and one astrocyte, which had a higher concentration of PLC δ, was put in a line. Then Ca^{2+} wave propagated from the cell periodically.

Our astrocytic $[Ca^{2+}]i$ model produced glutamate-induced $[Ca^{2+}]i$ responses, spontaneous $[Ca^{2+}]i$ oscillation in an astrocyte and intercellular Ca^{2+} wave. The results obtained from the model suggest that the translation quantity of PLC δ in an astrocyte will determine whether the astrocyte can have spontaneous $[Ca^{2+}]i$ oscillation or not, determine the refractory period of IP_3 -stimulated $[Ca^{2+}]i$ response and the waveform of $[Ca^{2+}]i$ oscillation. PLC δ in astrocytes is also important for Ca^{2+} wave to propagate through the cells. It is thought that PLC δ is a key molecule for astrocytic $[Ca^{2+}]i$ oscillation and wave.

Our model comes from De-Young and Keizer's $[Ca^{2+}]i$ model (1992) of non-excitable cells. It does not include plasma membrane Ca^{2+} channel. The astrocytes in our model thus don't have the volatage-dependent-inflow of Ca^{2+} from outside, while they have glutamate-induced $[Ca^{2+}]i$ responses, spontaneous $[Ca^{2+}]i$ oscillation and Ca^{2+} wave. Hence, Ca^{2+} entry from the extra cellular space may not be needed to induce the $[Ca^{2+}]i$ responses of astrocytes.

References

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