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Anomalous and Apparently Anomalous Diffusion in the Area of Neurophysiology

Elena Saftenku

A.A. Bogomolez Institute of Physiology, 4 Bogololetz St., Kiev, 01024, Ukraine
E-mail : esaft@biph.kiev.ua

1. Introduction

In the central nervous system information is transmitted from neuron to neuron due to functional contacts, or synapses, where a chemical intermediary, or neurotransmitter, releases following electrical signals in presynaptic cells; its binding to surface receptors triggers an influx of ions into the postsynaptic cells causing the shift of membrane potential away from the resting state. Glutamate releases in majority of brain synapses. The glutamate concentration time course in the synaptic cleft is influenced markedly by the geometry of the space that surrounds the synapse and the properties of glutamate diffusion in this geometry. Intracellular signals that lead to regulation of cell processes are transmitted by a limited number of small molecules, which are called second messengers. Their diffusion ensures the spreading of the signal all over the cell. Ca^{2+} is a unique molecule that relays signals mediated by membrane potential changes to the cell interior. Furthermore, in response to the binding of glutamate with metabotropic glutamate receptors, inositol 1,4,5-triphosphate (IP_3) is generated that releases Ca^{2+} from the intracellular stores.

Recently first communications that neurotransmitters in the extracellular space and second messengers in the dendrites of neurons can undergo anomalous diffusion appeared [1, 2]. Earlier diffusion kernel with fractional dimension was used for approximation glutamate diffusion in calyx of Held synapses [3]. Diffusion of IP_3 in the spiny dendrites was proven to occur owing to trapping of molecules in these structures [2]. Nevertheless the causes of anomalous diffusion of both IP_3 in smooth dendrites, and glutamate in the extracellular medium are not evident. Can the diffusion of neurotransmitters and second messengers be only apparently anomalous?

2. Simulation of glutamate diffusion and uptake in the extracellular space with complex geometry and IP_3 diffusion and degradation in smooth neuronal dendrites

Previously we have shown that glutamate diffusion in the cerebellar glomerulus, a structure where a mossy fiber (MF) terminal makes synapses with dendrites of granule cells (GrCs), was much better approximated by equation for fractional Brownian motion (FBM) than by normal diffusion equation and suggested anomalous diffusion of the neurotransmitter [1]. For some short period of time (up to 2 ms) this observation could be explained by normal diffusion of glutamate from a 2-dimensional (2D) cleft between the MF terminal and the surface of dendrites into a 3-dimensional (3D) porous medium with a low volume fraction. Some transitory region exists, where effective diffusion coefficient and dimensionality depend on *t*.

Nonlinear time-dependence of spatial variance can also arise from time-dependence loss of molecules owing to binding with immobile buffers, degradation, or diffusion into other dendrites if diffusion of species in theses structures is considered, but in this case a power-law relationship between variance and time is not observed.

It was shown that IP_3 in smooth dendrites diffuses with anomalous exponent 4.5. Intracellular binding and degradation were suggested to be candidates for such behavior [2]. To investigate this possibility, we developed a model of synaptically evoked Ca^{2+} elevations in smooth GrC dendrites. This model included the mechanisms of Ca^{2+} influx, release and buffering. The rates of IP_3 conversion to IP_4 via 3-kinase and their $[Ca^{2+}]_i$ dependence and to IP_2 via 5-phosphatase in range of experimental measurements were tested. The time constant of IP_3 degradation was much slower than the time course of IP_3 diffusion and could not produce anomalous diffusion behavior in our model.

Overcrowding of molecules causes anomalous diffusion only if molecules are large and have dimensions of dextrans or proteins in spite of significant retardation of the diffusion of both small and large molecules. IP_3 is a sufficiently small molecule with MW<0.5 kDa. Which physical processes can produce anomalous diffusion of IP_3 in smooth dendrites still remains unclear.

The other question, which we asked was if binding of glutamate transporters that are responsible for glutamate uptake from extracellular medium, can produce apparent anomalous diffusion. In the glomerulus transporters are situated on glial membranes at distance about 1.5 μm from the surface of MF terminal. The glutamate concentration transients were numerically integrated using a finite-difference method in an idealized model of glomerulus morphology. In our previous model [1] glutamate uptake was modeled by introducing an absorbing boundary for the diffusion field. In this work transporters that possessed kinetic properties of the transporter subtype GLAST of Bergman glial cells were included explicitly. Only the latest phase of currents mediated by glutamate spillover from neighboring release sites was influenced. Thus glutamate uptake by distantly situated transporters could not account for apparently anomalous glutamate diffusion. Glutamate buffers are not known and their existence is doubtful. Attachment plaques between dendrites could be considered as the sites of glutamate trapping, but their role is still ambiguous.

3. Conclusion

The causes of anomalous character of IP_3 diffusion in the smooth dendrites and glutamate diffusion in the extracellular medium of the cerebellar glomerulus still are not understood. Anomalous diffusion should be distinguished from the processes that resemble it. Our simulations show that IP_3 degradation or glutamate uptake by transporters could not produce anomalous diffusion behavior.

References

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