



The History of MS-Patch-Clamp Technique Development: Integration of Mass Spectrometry and Membrane Electrophysiology

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Abstract

The history of MS-patch-clamp technique development as integration of single-cell mass spectrometric and membrane electrophysiological instrumental approaches (from the integration of patch-clamp electrophysiology and capillary electrophoresis-mass spectrometry and primary MS-patch-clamp proposals to the novel single-lysosome mass spectrometry techniques (SLMS) and rapidly progressing area of combined single-cell-level mass-spectrometry and capillary electrophoresis for the analysis of activity of excitable living tissues) has been considered. The author expresses a desire for international collaborations to advance the development of MS patch clamp methods and related techniques in the future. The material of this short communication was initially planned as a presentation at the conference on mass spectrometry in 2024, but the inability to obtain a visa from Russia and financial difficulties associated with the international sanctions made this presentation impossible.

Keywords : MS-patch-clamp techniques; Ion channels; Patch-clamp electrophysiology; Capillary electrophoresis-mass spectrometry; Single-lysosome mass spectrometry techniques; Single-cell-level mass spectrometry; Single-cell proteomics; Single-cell metabolomics

Introduction

In 2021 the journal Nature Methods has published a brilliant paper "Metabolomics profiling of single enlarged lysosomes" [1], in which the authors, in particular, postulate that (quotation):

- “We therefore built a single-lysosome mass spectrometry (SLMS) platform integrating lysosomal patch-clamp recording and induced nano-electrospray ionization (nano-ESI)/mass spectrometry (MS) that enables concurrent metabolic and electrophysiological profiling of individual enlarged lysosomes”.
- “SLMS can open more avenues for investigating heterogeneous lysosomal metabolic changes during physiological and pathological processes”.

In this outstanding work, the authors have also cited our paper (ref. 22) "MS-Patch-Clamp" or the Possibility of Mass Spectrometry Hybridization with Patch-Clamp Setups for Single Cell Metabolomics and Channelomics" [2] (which is an extended version of our report given in 2014 at the conference “Structure and Functions of Bio-membranes” [3]) in the following context: "In recent years, several reports have suggested and verified the possibility of combining MS with patch-clamp recording for studying single-cell metabolomics (refs. 20-23)". It can be seen from the latter references that our work is among the pioneering ones in the area of integration of mass spectrometry and patch-clamp, since we are preceded only by the work on the integration of patch clamp electrophysiology and capillary electrophoresis-mass spectrometry [4], while the following works (including the landmark paper on the single-neuron identification of chemical constituents, physiological changes, and metabolism using mass spectrometry published in PNAS [5]) are the works of very productive Chinese authors (partly included in the author team of the paper [1]; see also the Supplement to this article). Indeed, we were the first in the Center for Mass Spectrometry of the Russian Academy of Sciences to propose the MS-patch-clamp concept, which has already emerged in 2010-2011 during the period of our working at the Geochemical Institute of the Russian Academy of Sciences in the laboratory equipped with mass spectrometers, and has been practically tested only in 2014. Subsequently our work has been cited in several papers including those published in *Angewandte Chemie* [6,7] and also has been used in a number of US and European grant proposals without our participation (e.g., see "Resolving Axonal Clearance using the Ubiquitylation Proteasome Pathway in Alzheimer's Disease (AD)" [8])

The Turning Point

Unfortunately, due to the reorganization of the Research Institutes of the Russian Academy of Sciences after 2013, we have not been able to continue these works for almost ten years. Our instrumentation is extremely outdated (most of the equipment was produced in 1980-2008, such as INCOS MS), so it is impossible to continue this work in Russia now (due to the almost complete absence of the single cell MS equipment). So, we would be happy to collaborate with our international colleagues who have already done everything and even more than we wanted to do about 10 years ago. However, we still have several ideas for the possible improvement and development of the above mentioned methods, and we are ready to share these ideas with them. It is noteworthy that Gradov O.V. tried to continue working on patch-clamp analysis even after the Institute reorganization, but without access to the mass-spectrometric equipment he had to focus on the application of the data analysis methods and other hardware-independent problems, publishing the previously obtained results in the Russian journals usually inaccessible to the international readership, as well as in the conference special issues [9-17]. This forced shift towards theoretical works and reviews resulted from the limited technical basis, leading to the impossibility of working in instrumentally monopolized science in the Russian Federation.

Conclusion

Nevertheless, many well equipped foreign laboratories to date are actively working in this new field and obtain intriguing results in the area of combined single-cell-level mass spectrometry and capillary electrophoresis for the analysis of activity of excitable

living tissues [18-29]. Unfortunately, the most remarkable papers in this area are aimed at the single-cell-level proteomics rather than at time-resolved spatiotemporal registration of the ion channel activity and transmembrane transport processes (which were the main aims of our initiative non-profit and non-funded project [30]). Therefore, the most interesting works and technical findings in this field are expected in the nearest future.

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