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Reply to "Letter to the editor: 'The use of extracellular, ion-selective microelectrodes to study the function of heterologously expressed transporters in *Xenopus* oocytes'"

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REPLY: The history of science shows that discoveries are generally the result of a chain of studies that build on one another over long time periods. In their letter to the editor, M. D. Parker, R. Musa-Aziz, and W. F. Boron (4) argue that the technical approach that we named "the ion-trap technique" in a recent article published in *American Journal of Physiology-Cell Physiology* (1) has been used in the past by their group in 2006 (2) as well as by de Hemptinne and Huguenin in 1984 (3). These three articles have in common the use of a large ion-selective electrode (ISE) to measure local ionic concentrations on the surface of isolated rat soleus muscle (2) or the surface of *Xenopus laevis* oocytes (1, 3). We have indeed cited the work of Endeward et al. (2) in our article together with three other articles, among several others, that could have been cited for their use of ISEs to measure extracellular ionic concentrations in different cell preparations. Our article was accepted for publication in *American Journal of Physiology-Cell Physiology* because the editor and the reviewers agreed that we were adding something new to a technique already used by other laboratories. The dimension that we added is the improved time resolution. The two articles cited (2, 3) report steady-state measurements, and the typical time scale used in their figures is 10 to 30 min. To bring the technique to another level in terms of time resolution, we increased the size of the ISE up to 100 μm in diameter. ISE with tip diameter of ~15 μm like those used by Endeward et al. (2) are adequate for steady-state measurements (and we have used them for this purpose in our article) but are characterized by resistances on the order of 1 GΩ, a larger noise level, and a long rise time. The typical electrode we used presents a resistance of 0.1 GΩ and a rise time of 20 ms.

In our article (1), we spent a great deal of effort establishing that the slope (often less than 1 mV/s) and the step (10 to 40 μV) that we detected during a 150-ms voltage pulse were both real and meaningful. Most of the figures presented in our article deal with different aspects of the pre-steady-state activity. Our main observation is that application of a voltage pulse produces a reorientation of the transporter binding sites, which is associated with a measurable amount of ions that are rapidly released or taken up from the trap.

In our view, expanding extracellular ionic concentration measurements to the millisecond range was a significant improvement to the way the technique had been used before, and we reasoned that it would be useful to give this approach a name instead of referring to it as the measurement-of-extracellular-ion-concentrations-using-a-large-ion-elective-electrode. This was not meant to belittle the past contributions of other researchers in the field.

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