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IS IT POSSIBLE TO DESIGN ISOTOPIC MASS-DEPENDENT MS-PATCH-CLAMP AND ISOTOPIC MASS-INDEPENDENT ESR-PATCH-CLAMP?

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Abstract. This paper is a comprehensive review of the possibilities of isotopic patch-clamp and isotopic mass-patch-clamp technique development and represents a brief summary of the student's tutorial review by S. Pankratov. We propose to distinguish between the mass-dependent and mass-independent patch-clamp. The main principles introduced here will be developed in details at the second part of this paper.

Keywords: mass-dependent isotope effect, mass-independent isotope effect, mass spectrometry, electron spin resonance spectroscopy, electron paramagnetic resonance spectroscopy, (radio)isotope measurements, spin label, patch-clamp.

Towards the mass-dependent isotopic patch-clamp

It has just been established that ion channels of the living cell can be studied using nuclear magnetic resonance (NMR) spectroscopy with isotope labeling (Abarca-Heideman, 2013) (for example, a number of simple bacterial channels, such as the potassium channel (Bhate, 2013), can be labeled for NMR). It is now evident that channelome (i.e. a complete set of the membrane ion channels in a biological tissue (Hoffert, 2009; Barrett-Jolley, 2010; Publicover, 2012)) is a labile isotopic-dependent system. These objects are known to be quite complex, although there are many approaches to their investigation. In addition to NMR labeling, it is also possible to use either Fourier transform infrared (FTIR) difference spectroscopy for isotopic study of the membrane channels and receptors (a combination of different agonists and antagonists along with the structural changes upon isotopic labeling results in the band shifts in their infrared (IR) spectra) (Baenziger, 1993) or mass-spectrometric methods, aimed for the atomic mass determination, and hence, the isotope mass analysis.

Some early investigators considered the deuterium isotope effect on permeation and gating of H^+ channels in the rat alveolar epithelium (DeCoursey, 1997). This effect becomes even more marked when using heavy radioisotopes, but it is very little known in such areas as «isotopic membranology» and, moreover, «isotopic channelomics». We shall assume that the reader has an idea of mass-spectrometric isotopic label determination in membrane structures, since it has long been known that mass spectrometry is an optimal tool for membrane component and constituent analysis (such as lipids (Schneiter, 1999; Gerl, 2014; Pannkuk, 2014), propeptides (Parker, 2014), membrane proteins and lipoprotein complexes (Souda, 2011; Marty, 2012; Morgner, 2012; Hopper, 2013; Laganowsky, 2013; Han, 2014)), including their labeled forms (Ruseva, 2014; Trompelt, 2014). A vast amount of technical data is provided by the stable isotope biochemical labeling (Pettelkau, 2013; Sparbier, 2013; Tang, 2013; Torde, 2013; Zhou, 2013; Dong, 2014; Herath, 2014; Huege, 2014; Liu, 2014; Popova, 2014; Wang, 2014) (including isotope-coded labeling (Gaupels, 2012; Kellermann, 2012; Biniossek, 2013; Rainczuk, 2013; Vogt, 2013; Hägglund, 2014; Pan, 2014), known since late 1990-s (Gygi, 1999) and optimally compatible with different mass spectrometry (MS) technologies (Han, 2001; Smolka, 2002; Turecek, 2002; Goshe, 2003; Tam, 2004; Hochleitner, 2005; Molloy, 2005; Schrimpf, 2005; Allison, 2006; Shiio, 2006; Kozarova, 2007; Sethuraman, 2007; Haqqani, 2008; Dong, 2011), such as GC-MS (Zhong, 2012), LC/MS (Li, 2004; Dall′asta, 2005; Prokai, 2005; Yu, 2007; Turtoi, 2010; Guo, 2012; Toyo′oka, 2012), LC-MALDI (Jochim, 2011), comparative MALDI and MALDI-TOF (Tsumoto, 2007; Nelson, 2008; Koulman, 2009), 2-DE/MS (Kim, 2006), LC-MS/MS (Shen, 2007; Manini, 2010), tandem MS, including liquid chromatography-tandem mass spectrometry (Haller, 2003; Haller, 2003a; Yan, 2004; Li, 2005; Moulder, 2005; Qu, 2006; Vaughn, 2006; Butler, 2007; Zhang, 2013), quadrupole ion trap MS (Seo, 2007) etc.), nonstable isotope labeling (see, for example, (Lappin, 2010; Zhang and Katta, 2012; Grunwald, 2013) and the corresponding MS methods, known as «accelerator mass-spectrometry» (Hah, 2009; Salehpour, 2009; Lappin, 2010)) used as the metabolic and chemical structure labeling methods (Schmidt, 2014). Isotope labeling methods are indispensable tools for organic and bioorganic chemistry, which can be applied to membrane proteins, ion channels, receptors, glycolipid intercalates and other membrane structures, particularly those biochemically involved in the patch-clamp techniques.

It is also known that the methods for mass-spectrometric studies of the membrane proteins (Barrera, 2011; Was, 2014), membrane protein complexes (Barrera, 2011; Hopper, 2013) and transmembrane domains (Eichacker, 2014; Gerl, 2014) can be applied together with the selected ion recording system, based on the mass-spectrometric principles for a precise isotope ratio determination in biomedical assays when the single isotope enrichment is derived from a single label (Gruenke, 1980). The above analysis suggests a conclusion that the significance of the MS-methods for biochemical isotope ratio determinations of the membrane constituents or components can be considered as the prerequisite of the possibility of the *in situ* isotopic measurements based on

or combined with the path-clamp-like principles. This conclusion is not applicable for multi-isotope mass-spectrometry, including multi-isotope mass-spectrometric imaging (McMahon, 2006; Alexandrov, 2011; Gormanns, 2012; Goto, 2012; Lechene, 2012; Steinhauser, 2012; Zhang, 2012; Steinhauser, 2013) using liquid pumping and adjustable capillary systems similar to those used in the standard patch-clamp configuration (Chen, 2008; Chen, 2010). Earlier we have already shown the possibility of the MS-patch-clamp techniques (Gradov, 2014; Gradov, 2015), but those theoretical considerations failed to provide reliable results without strong biochemical argumentation in the frame of the biophysics of the isotope-labeled agents, such as receptors, antagonists, blockers, transmitters, etc. From the above considerations one can conclude that selective amplification of the isotope uptake by the electrical diffusion potentials is a direct consequent of the ion channel-mediated flux occurring in the membrane vesicles (Garty, 1989) and the isotope flows and flux ratios in biological membranes, which are interrelated (Kedem, 1965) as in the ion exchange membranes (DeSousa, 1971; Li, 1974).

In consistence with the above approach we should list some classical objects which are used for different isotopic membranological studies as the targets and labeled / labeling compounds or visualizing agents: receptors (Pisani, 2002), receptor agonists (Rubovszky, 2003), labeled receptor inhibitors (Kapras, 2012), receptor antagonists (Thominiaux, 2006), receptor mapping agents (Gildersleeve, 1996) and neurotransmission agents visualized by PET imaging (Martin, 2013), radioligands for ion channels (Gould, 1983; Lovenberg, 1986; Marvinzon, 1988; Rauh, 1997; Fuchigami, 2012) / receptors (Jones, 1989; Pike, 1993; Rubin, 1993; Veghel, 2013), pharmacodynamic brain occupancy substances of receptor inverse agonists (Laere, 2014), channel openers (Davis-Taber, 2003), stimulants, based on neurotransmitter injection activation principles (and their precursors) (Salouros, 2013), ion channel activity reconstitution and membrane binding agents (Hamilton, 1989), etc. A problem which frequently arises from the variety of the above agents is a distinction between the mass-dependent and mass-independent isotope effects in the metabolic and other reactive redox-systems, including photolytic, thermal and electrolytic ones (Cole, 2006; Bergquist, 2007; Bhattacharya, 2009; Fujii, 2009; Sun, 2011; Jackson, 2012), which particularly can be distinguished by the mass-spectrometric methods, predominantly Inductively coupled plasma mass spectrometry (ICP-MS) both in mass-dependent (Anbar, 2001; Dauphas, 2004; Ohno, 2007; Ohno, 2013) and mass-independent (Dauphas, 2004; Cook, 2006; Malinovsky, 2011; Yang, 2011) variants, despite the fact that the cited works are mostly devoted to the isotope fractionation as the most abundant isotopic effect.

Towards the mass-independent isotopic patch-clamp

Another reasons lead to the idea of the mass-independent isotope effect-based patch-clamp studies and measurements with the main problem of the mass-independent isotope registration.

The most relevant contribution to the mass-independent isotope effect theory was made by A.L. Buchachenko (Buchachenko, 2013). The theory of the mass-independent isotope effect (also known as «magnetic isotope effect») proposed and developed by A. Buchachenko has been applied to a number of biochemical processes and objects, including the synthesis of semantids (Buchachenko, 2013a; Buchachenko, 2013b), enzymatic ATP synthesis (Buchachenko, 2008; Buchachenko, 2008a; Buchachenko, 2010; Buchachenko, 2012) and intramitochondrial phosphorylation (Buchachenko, 2004; Buchachenko, 2005; Buchachenko, 2005a), ATP synthase efficiency as a molecular machine and magnetic mechanochemistry of the phosphorylating agents (Buchachenko, 2005b; Buchachenko, 2006; Buchachenko, 2008b; Buchachenko, 2008c). It has been noted that the magnetic magnesium isotope delivered by the membranotropic cation-exchanging fullerene-based nanoparticles into the myocardial cells is capable of the hypoxia-caused metabolic acidosis treatment by means of the reactivation of ATP synthesis, and thus, provides

normalization of both intracellular proton concentration and the heart muscle cell membrane potential (Amirshahi, 2008; Rezayat, 2009; Shetab Bousheri, 2010). This is a remarkable fact, because the membrane potential is usually measured by electrophysiological methods and, moreover, patch-clamp is a classical selective technique for the single ion channel recordings on cardiomyocites (Richardson, 2010; Honda, 2011; Stoelzle, 2011; Schroder, 2012). It is even more rational to combine this method with the magnetic techniques for mass-independent / magnetic isotope effect registration. This goal can also be achieved by means of the exotic hybridization of the single calcium channel registration and the electron spin resonance spectral studies, whereof Wang Xiaoming with coauthors suggests that this complex approach may have a practical application for the registration of the calcium channel blocking effect on ventricular myocytes (Wang, 1994).

Although this method is a non-conventional one, it can provide valuable information. Another essential method applied in Buchachenko's approach was the single-spin ESR (electron spin resonance) along with the other ESR methods (Buchachenko, 2001). The former method differs significantly from the latter one, but the general principle for spin label measurements is the same in both works, and thus it can be applied for the spin labeled ion channel recording.

For example, from the beginning of the ESR-technique development, biophysicists have accepted the spin labeling technique for the simplest ion channels, such as spin-labeled derivatives of gramicidin peptides (Ivanov, 1973) and spin-labeled gramicidin itself (Dzikovski, 2011), labeled valinomycin and its analogs (Ivanov, 1974) (along with the NMR observations of the nuclear Overhauser effect of transfer of the nuclear spin polarization from one nuclear spin population to another one via cross-relaxation (Glickson, 1976; Krishna, 1978); the same method has been applied to the gramicidin (Jones, 1978; Huang, 1981; Barsukov, 1987), cecropin (Mchaourab, 1993; Mchaourab, 1994; Hung, 1999; Bhargava, 2004), zervamicin (Milov, 2002; Milov, 2010) (early labeled by deuterium (Ogrel, 1997), ^{13}C and ^{15}N for NMR measurements (Ovchinnikova, 2003)), alamethicin (Archer, 1991; Crisma, 2007; Marsh, 2007; Bartucci, 2009; Marsh, 2009), etc. It is noteworthy that gramicidin as well as valinomycin (Gliozzi, 1996) are well known as the simple ion channels (Hu, 1993; Haldar, 2012; Wang, 2013; Basu, 2014; Chaudhuri, 2014), which can be studied by spin labeling and magnetic resonance methods (Planque, 1998; Dzikovsky, 2004), as well as ion-channel-forming valinomycin (Eastman, 1974; Meers, 1988; Kriz, 2006); zervamicin is also well known as the ion-channel-forming agent, ion channel peptide and a good model for the membrane ion channels (Agarwalla, 1992; Sansom, 1993; Ovchinnikova, 2007) with a well-studied gating mechanisms (Karle, 1991; Ballesteras, 1992; Karle, 1994) which can operate not only in the native membranes, but also in the artificial micelles and lipid bilayers (Shenkarev, 2002), and can be studied using spin labeling ESR approaches as well as other equivalent mechanisms (Barranger-Mathys, 1996; Perozo, 2001; Dellisanti, 2013); colicin (also studied by spin labeling and ESR (Todd, 1989; Shin, 1993; Pulagam, 2013)) also well known as the ion channel-forming protein (Ghosh, 1994); cecropins (also studied by the spin labeling and ESR (Mchaourab, 1993; Mchaourab, 1994; Hung, 1999; Bhargava, 2004) and NMR (Holak, 1988; Sipos, 1991; Sipos, 1992; Marassi, 1999; Oh, 1999; Yagi-Utsumi, 2013)) known as the ion channel-forming peptide (Juvvadi, 1996; Bechinger, 1997) and a simple ion channel model compound incorporated into planar lipid membranes for membrane biomimetics (Christensen, 1988), based on the objective model approaches (Durell, 1992).

It is noteworthy that many membrane channels, receptors and other membrane structures are Mg^{2+}-dependent, while its isotopes were used in the studies performed by A.L. Buchachenko and his coauthors (Amirshahi, 2008; Rezayat, 2009; Shetab Bousheri, 2010). Thus, it is well accepted that CorA is the major transport system responsible for Mg^{2+} uptake in bacteria and can functionally substitute its homolog Mrs2p in the yeast inner mitochondrial membrane (Dalmas, 2014). There are also conformational changes in a GAAA tetraloop receptor upon Mg^{2+}-dependent conditions (Qin, 2005). Despite the receptors and transducers which are Mg-dependent structures at the molecular

level, one can also give an example of the Mg-dependent phase, microhydrodynamical and rheological properties of the membranes at both micro- and mesoscopic levels (Ogiso, 1981; Yang, 1983; East, 1984; Sorensen, 1987). Due to the effects coupled with ATP, AMP, adenylate cyclase activators (Du, 1982; Yang, 1988; Zhang, 1989; Coan, 1993; Negash, 2000; Zimmermann, 2000) Mg^{2+} participates in the membrane bioenergetics. Since different metal ions (Fe^{2+}, Cu^{2+}, Ca^{2+}, Mg^{2+}) influence the transmembrane transport differently (Lohmann, 1986), to date it is possible to postulate the existence of a direct relationships between the membrane metallomics (Klein, 2011) of Mg^{2+} with the membrane bioenergetics. It should be noted that the above idea is also applicable to the photosynthetic bioenergetical structures, since there has been reported an effect of the magnesium ions on the structural state of the thylakoid membranes and the kinetics of the electron transport between the two photosystems in bean chloroplasts (Tikhonov, 1980), and it was also found that Mg^{2+}-induced lipid phase transition in the thylakoid membranes can be reversed by the anions (Jajoo, 1994). Similar Mg-dependent mechanisms determine the bioenergetics in the sarcoplasmic reticulum membranes by magnesium-dependent adenosine triphosphatase (Kirino, 1978).

Hence, it is not surprising that Mg^{2+} is widely involved in the biochemical pathways as a cross-agent and / or a physiological indicator in spin labeling methods (in particular – with nitroxyl (Du, 1982) and biosynthetically generated phospholipid spin labels (Takeuchi, 1981)). For the neurons being classical objects for the patch-clamp experiments, spin labels are frequently used (including the studies of the anesthetic effects upon the membrane (Wang, 1982)). At the same time it is obvious that divalent cations, including Mg^{2+}, significantly affect the results of the spin label studies of the brain membranes (Viret, 1976), as well as other biomembranes in the context of their biosynthetic and bioenergetical activity, e.g. in *Esherichia coli* (Takeuchi, 1978). A classical ion channel – valinomycin, under NMR studies of its membrane-associated location and ion-binding demonstrates an interesting effect in presence of the bivalent ions: Rb^{+} and K^{+} show 1:1 binding to valinomycin, whereas the stoichiometry of Cs^{+} and Ba^{2+} is not certain (Meers, 1988). This fact is of great importance, since the investigation of the surface potential in phospholipid vesicles by a spin label relaxation method reveals the coupling between the surface potential asymmetry and the parameters measured using spin labeling (Sundberg, 1986), as well as the dependence of the transmembrane electrical currents on the differently charged spin-labeled hydrophobic ions (Cafiso, 1982). The above considerations suggest that it is reasonable and necessary to develop mass-independent isotopic patch-clamp, including its variation combined with the magnetic ESR measurements and spin labeling techniques. This can be illustrated by an example of the postsynatpic membrane acetylcholinesterase and acetylcholine receptors of the electric organ of *Torpedo marmorata*. Transmembrane potential of the postsynatpic membrane can be considered as the source of the surface bioelectrogenesis of Torpedo marmorata electric organ, i.e. to be a subject of the high-voltage electrophysiology and EHV patch-clamp / voltage clamp. At the same time it is possible to perform ESR study of the postsynatpic membrane acetylcholinesterase of *Torpedo marmorata* electric organ (Sentjurc, 1976) and of the association of the spin-labeled local agents at the hydrophobic surface of acetylcholine receptor in the native membranes from *Torpedo marmorata* (Horvath, 1990) or of the effect of general anesthetics on the lipid-protein interactions in acetylcholine receptor enriched membranes from *Torpedo nobiliana* using nitroxide spin-labels (Frazer, 1990). Considering that since 1970–1980-th patch-clamp studies (Fenwick, 1982; Akaike, 1984; Allen, 1984; Gallacher, 1986; Methfessel, 1986; Brett, 1988; Kuba, 1989; Pennington, 1990; Nooney, 1992; Milone, 1994; Buisson, 1996; Keleshian, 2000; Re, 2003; Matsubayashi, 2004; Robertson, 2013; Hao, 2015) and voltage clamp studies (Sano, 1970; Anderson, 1973; Bolton, 1975; Sachs, 1977; Fischbach, 1978; Bregestovski, 1979; Chad, 1979; McCandless, 1981; Wachtel, 1981; Takeyasu, 1983; Hirano, 1987; Woody, 1987; Cachelin, 1989;

Nelson, 1992; Simon, 1992; Voigt, 2010) on acetylcholine or its functionally complementary agents, therefore a similar patch-clamp / voltage-clamp approach is particularly applicable to the electrogenerating membrane structures, including neuromimetic ones. From the standpoint of molecular biomimetics and QSAR / QSPR (quantitative structure–activity relationship / quantitative structure–property relationships) it is interesting to mention that ESR studies using different spin labeled acetylcholine analogs are frequently used in the studies of the cholinergic receptor (Rosen, 1975).

Another advantage of the Buchachenko's approach is the possibility to work with the singlet molecular oxygen (Martinez, 2005; Buchachenko, 2006a; Buchachenko, 2011), including the studies on the photo-oxidation of water by molecular oxygen considering the isotope exchange and isotope effects (Buchachenko, 2011). The method described in the above cited paper can also be applied to the studies of the light-induced hindrance of spin label motion in the lumen of spinach thylakoids (Nesbitt, 1980) using patch-clamp techniques, since modern patch clamp techniques for studying the ion channels in organelles (Keller, 1992) allow not only to perform a patch-clamp study of the vascular plant chloroplasts (Muniz, 1995), but also a patch-clamp study of the voltage-dependent anion channel in the thylakoid membrane (Pottosin, 1995). This makes possible in future to apply ESR magnetic isotope patch-clamp method for studying the activity of the oxygen channels (Ivanov, 2007; Frankel, 2012) and oxygen sensitive channels (Lopez-Barneo, 2004; Otsubo, 2006). The implementation of the above technique with the ESR setups equipped with a capillary connected to the standard patch-clamp registration system is not difficult, since the detection of the singlet oxygen (Schaich, 1976; Cannistraro, 1977; Moan, 1979; Feix, 1991; Song, 1999; Lavi, 2004; Jung, 2009), as well as the other reactive oxygen species (Capani, 2001; Kasazaki, 2003; Yamato, 2003; Cao, 2005; Xu, 2007; Sawada, 2010; Saita, 2012; Lee, 2013; Qi, 2016) within their physiological and biochemical functions in the cellular structures, is long performed using ESR methods.

It is also possible to combine the conventional isotope and ESR studies by using the isotope label method (isotope-substituted, membrane-impermeant bifunctional spin label for the studies of the dynamics of the membrane proteins; for example, in application to the anion-exchange channel (Anjaneyulu, 1988)). It should be also mentioned here that the oxygen isotopes have been already used for a long time as the labels in molecular biology and biophysical chemistry, being the classical research tools with ^{18}O (Burstein, 1974; Puzo, 1977; Sleep, 1978; Marnett, 1979; Hackney, 1980; Pickett, 1981; Rosenberg, 1981; Rosenberg, 1981a; Stempel, 1986; Ponnusamy, 1986; Aissa, 1988; McLeish, 1989; Risley, 1989; Murphy, 1990; Tian, 1994; Horvitz, 2001; Martinez, 2002; Ye, 2003; Staes, 2004; Crean, 2005; Niles, 2009; Schliep, 2010; Fernandez-de-Cossio, 2011; Melby, 2011; Qian, 2011; Kanady, 2013; Sha, 2014; Stingl, 2014) being more popular than ^{15}O (West, 1968; Subramanyam, 1977; Berridge, 1986; Berridge, 1990; Moerlein, 1993) and other ones.

This suggests the possibility to apply them for the studies of the oxygen- and redox-dependent ion channels, as well as for the analysis of their redox regulation (Elliott, 1997; Carpaneto, 1999; Anzai, 2000; Choudhary, 2002; Hall, 2003; Matalon, 2003; Wang, 2003; Buck, 2004; Schön, 2005; Antonenko, 2006; Tsikolia, 2009; Petrotchenko, 2011; Fogle, 2015), including the classical Marinov ion channel redox model (Marinov, 1991), and hence, a redox-dependent voltage clamp (Hoffman, 1976; Hescheler, 1989; Puppi, 1991; Haddad, 1993; Shattock, 1993).

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