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ORIGINAL ARTICLE

Membrane Fluidity Changes, A Basic Mechanism of Interaction of Gravity with Cells?

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Abstract All life on earth has been established under conditions of stable gravity of 1g. Nevertheless, in numerous experiments the direct gravity dependence of biological processes has been shown on all levels of organization, from single molecules to humans. According to the underlying mechanisms a variety of questions, especially about gravity sensation of single cells without specialized organelles or structures for gravity sensing is being still open. Biological cell membranes are complex structures containing mainly lipids and proteins. Functional aspects of such membranes are usually attributed to membrane integral proteins. This is also correct for the gravity dependence of cells and organisms which is well accepted since long for a wide range of biological systems. However, it is as well established that parameters of the lipid matrix are directly modifying the function of proteins. Thus, the question must be asked, whether, and how far plain lipid membranes are affected by gravity directly. In principle it can be said that up to recently no real basic mechanism for gravity perception in single cells has been presented or verified. However, it now has been shown that as a basic membrane parameter, membrane fluidity, is significantly dependent on gravity. This finding might deliver a real basic mechanism for gravity perception of living organisms on all scales. In this review we summarize older and more recent results to demonstrate that the finding of membrane fluidity being gravity dependent is consistent with a variety of published laboratory experiments. We additionally point out to the consequences of these recent results for research in the field life science under space condition.

Keywords Gravity perception · Membrane fluidity · Alamethicin · Space pharmacology

Introduction

Biological cell membranes are complex structures containing mainly lipids and proteins (i.e. Pollard and Earnshaw 2008). Functional aspects of such membranes are usually attributed to membrane integral proteins. However, biological membranes may be also understood as two-dimensional thermodynamical systems, which can be described by temperature, pressure and area. Usually temperature and area are taken to be more or less constant in biological cell membranes, at least on a short time scale. To probe the influence of the lateral membrane pressure, or in other words membrane fluidity, on the properties of biological systems is not trivial, but in numerous experiments it has been clearly verified (DePietro and Byrd 1990; Hanke and Schlue 1993; Zanello et al. 1996). Thus, it is well established now that physical parameters of the lipid matrix are directly modifying the function of proteins (Dowhan and Bogdanov 2002; Edidin 2003; Jamey and Kinnunen 2006). More specifically this has been discussed also in dependence of lipid composition of membranes, which is known to be a strong modulator of membrane fluidity (i.e. Spector and Yorek 1985; Tillman and Cascio 2003). Additionally, the

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medical and pharmacological relevance of membrane fluidity changes has been clearly demonstrated (Graesboell et al. 2014; Riede 2014; Zhou et al. 2015). Especially the influence of a wide variety of drugs has been described in deep detail since long (i.e. Goldstein 1983; Heimburg and Jackson 2006).

It also has then been discussed in some detail, whether membrane fluidity might serve as a direct sensor for the perception of environmental signals (Murata and Los 1997; Mikami and Murata 2003; Los and Murata 2004), as there are temperature (Catala and Salianas 2010), and osmolarity, but also its relevance for quorum sensing has been mentioned (Baysse et al. 2005). By changing membrane fluidity by external parameters, in a second step, protein associated functions then will be modified and serve as sensor for external signals.

Having now a look at gravity as an external environmental signal, it is obvious that usually on earth no changes in 1g have been given for geological periods. However, in space-flight experiments the question of sensing gravity is of essential importance. It is known that higher organisms, from plants to humans, have developed a variety of specialized organs and systems to sense gravity. Most of them are well understood, as there are for example the gravitropism of plants (i.e. Blancafloror 2015; Chen et al. 1999) or the inner ear of humans (Anken and Rahmann 2002). However, it also has been shown that even single cells with, or also without any specific known mechanism, can sense gravity, a finding not being understood completely until lately (Häder et al. 2006, 2017; Wiedemann et al. 2003; van Loon 2009; Nickerson et al. 2004).

Recently, some experiments have been published, delivering somewhat more detailed information about membrane fluidity directly serving as sensor for gravity, these findings then also verifying some older and previous experiments already rising the same question.

Results

In some experiments discussing the effect of microgravity on mechanically-induced membrane damage in 2001, already it has been indirectly argued, but not been well proven, that membrane order might been changed by microgravity (Clarke et al. 2001). In parabolic flights, the authors found that membrane wounding and repair are affected by gravity. Especially repair was partially inhibited, and they argued that this might be due to the influence of gravity on membrane order parameters including fluidity. Van Loon argued (2009) in this direction, when he stated that mechanical modifications of cell membranes might be responsible for a variety of responses of biological systems to gravity changes.

In other studies, directly the influence of altered gravity on the membrane fluidity of pea root plasma membranes (Klymchuk et al. 2006) and on plant cytoplasmic membranes (Kordyum et al. 2015) has been investigated in clinorotation experiments (Klymchuk et al. 2006) and it has been proposed that clinorotation increases membrane fluidity. Although there are still some questions open about the equivalence of real microgravity and clinorotation, this also supports the relevance of membrane fluidity for gravity sensing.

Lately it has been shown now directly in plane lipid vesicles and in real cell membranes that membrane fluidity is depending on gravity, increasing towards lower gravity values, using the fluorescent dye DPH as sensor (Sieber et al. 2014). Previously, in drop tower experiments, it had been shown that under micro-gravity the size of plain lipid vesicles slightly increases (Meissner et al. 2004). Due to the direct functional dependence of membrane area and lateral membrane pressure, this now can be interpreted, and is better understood, in a change of lateral membrane pressure towards lower values at microgravity. Again this shows, membrane fluidity increases towards lower gravity values. In addition, in neuronal cells, direct changes of membrane fluidity were reported (Sieber et al. 2014) using a high throughput plate reader technology (Kohn 2013).

Another recent finding is that current fluctuations induced in plain lipid bilayers by high potential (Bilcher and Heimburg 2013) are reduced under microgravity (Sieber et al. 2016). Again this has been explained by a higher membrane fluidity, which either leads to smaller leaks in membranes or allows a faster healing of leaks in the lipid membrane (see also: Clarke et al. 2001). The finding that membrane fluidity is involved significantly in the resealing of perforated membranes is supported additionally by electroporation experiments (Kanduser et al. 2006). In the experiments performed in parabolic flights (Sieber et al. 2016), gravity induced changes in bilayer capacity due to limited resolution of the recording technology and geometrical changes of the bilayer could not clearly be demonstrated. A small increase in bilayer capacity would have been expected towards microgravity as at higher fluidity the membrane becomes thinner due to the higher mobility of the fatty-acid chains of the lipids, thus capacity increases. However, in earlier experiments at macro-gravity done in centrifuge experiments (Wiedemann et al. 2003), a slight increase of bilayer capacity at increasing gravity was shown. A final explanation of the capacity changes in membranes due to interaction with gravity is still open.

Especially in planar lipid bilayer experiments, alamethicin (Jung et al. 1981; Woolley und Wallace 1992; Leitgeb et al. 2007) incorporated into these, was used as a sensor to monitor the gravity dependence of membranes. This is due to the mechanism of pore formation, the so called

barrel-staff model, which is explicitly sensitive to membrane fluidity (Boheim et al. 1983; Mak and Web 1995). It was shown in a double film balance experiment (Langmuir-Blodgett-trough) that an increase in lateral membrane pressure, which is equivalent to a decrease in fluidity, in an elsewise plain lipid system increases the activity of alamethicin fluctuations (Hanke and Schlue 1993). Additionally, as found in some experiments at decreasing temperature, meaning at decreasing membrane fluidity, in planar lipid bilayers, alamethicin activity increases, too (Boheim et al. 1980), which in this case is due to a enriched alamethicin concentration in the fluid phase in the range of the phase transition temperature of the lipid used.

Also, alamethicin has been used as a general sensor for membrane properties (Steller et al. 2012) and as a sensor to directly monitor pore activity changes under changing gravity conditions (Klinke et al. 2000; Wiedemann et al. 2003). In such experiments it was shown that alamethicin activity increases towards higher gravity and decreases towards lower gravity (Wiedemann et al. 2003).

Up to here, the cited results agree quite well. Alamethicin activity in lipid membranes increases towards higher pressure and higher gravity, and membrane pressure (directly being related to membrane fluidity) increases towards higher gravity. Nevertheless, it has to be kept in mind that the interaction of gravity with alamethicin induced membrane activity is more complex. Not only the amplitude of applied gravity, but also the angle of gravity relative to the membrane surface has been shown to be effective (Wiedemann et al. 2003).

Because of the cited findings, additional questions must be asked, related to the incorporation of alamethicin in membranes. It has been shown in monolayer experiments that the incorporation of alamethicin in these is depending on the lateral pressure of the monolayers (Volinsky et al. 2004). The lateral pressure of monolayers and membrane fluidity are strictly related, thus, according to the gravity dependence of membrane fluidity the incorporation of alamethicin in vesicle membranes should be gravity dependent, too. Following this idea, finally, in a parabolic flight campaign, we have shown that the incorporation of alamethicin into planar lipid bilayers indeed is depending on gravity, it is slightly increased at microgravity (to be published). Having in mind the basic model of alamethicin pore formation, the barrel staff model (i.e. Boheim et al. 1983; Cafiso 1994; Pieta et al. 2012), finally a dependence of alamethicin pore state conductances on membrane fluidity, and thus on gravity, has to be questioned. In a preliminary data evaluation of older data (Klinke 1999; Wiedemann et al. 2003) it was found that pore state conductances slightly decrease towards increasing macro-gravity. This would be consistent with the barrel staff model of a variable number of parallel oriented alpha-helices to form the open alamethicin pores states.

Consequences

At first, as membrane fluidity of plain lipid bilayers and of cell membranes is directly gravity dependent (i.e. Sieber et al. 2014), any cell and thus any biological system has at least some residual gravity sensation since it exists. The consequences in understanding the evolution of life on earth and possibly under different gravity conditions in other locations beyond earth have to be taken into account in future (astrobiological) considerations.

Following the above already mentioned point that membrane fluidity directly effects the function of integral membrane proteins (i.e. Zanello et al. 1996; Seeger et al. 2010; Moosgard and Heimburg 2013), all membrane processes related to these will become gravity dependent. This does for example include the complete chemical synaptic transmission (Zanello et al. 1996), the behavior of ion channels (Goldermann and Hanke 2001; Wiedemann et al. 2011), the parameters of action potentials (Meissner and Hanke 2005) and others more as has been shortly mentioned in the introduction.

Furthermore, a variety of questions related to later manned human space missions must be discussed in more detail having the above statements in mind. Especially questions of pharmacology related to longer lasting human space missions are affected (Pavy-Le Traon et al. 1997; Idkaidek and Arafat 2011; Wotring 2012). It is known from numerous experiments that the pharmacological effects of hydrophobic and amphiphilic substances are depending on membrane fluidity as their incorporation into membranes is membrane fluidity dependent (i.e. Aloia and Boggs 1985; Volinsky et al. 2004). A large number of pharmacological relevant substances belongs to this physico-chemical class, i.e. anesthetics, steroids, antibiotics and others, and it has been shown for example in partitioning experiments that their incorporation in liposomes is among others membrane fluidity dependent (Liu et al. 2001).

Additionally, as integral membrane proteins in general are affected by membrane fluidity, their function in principle will be at least slightly gravity dependent. As an example, the binding of ligands to membrane receptors might be gravity dependent, as it has been already clearly shown that it is membrane fluidity dependent (DePetro and Byrd 1990; Tillman and Cascio 2003; Fernandes Nievas et al. 2008; Lohse et al. 1985). By this, another significant number of additional drugs would be included into the group of those being possibly gravity dependent in their activity (for example, 40 to 60% of all relevant drugs are substances affecting 7-transmembran-helix receptors).

The consequences of the presented results for possible long lasting human space mission are obvious and should give rise to increasing research activities in the field.

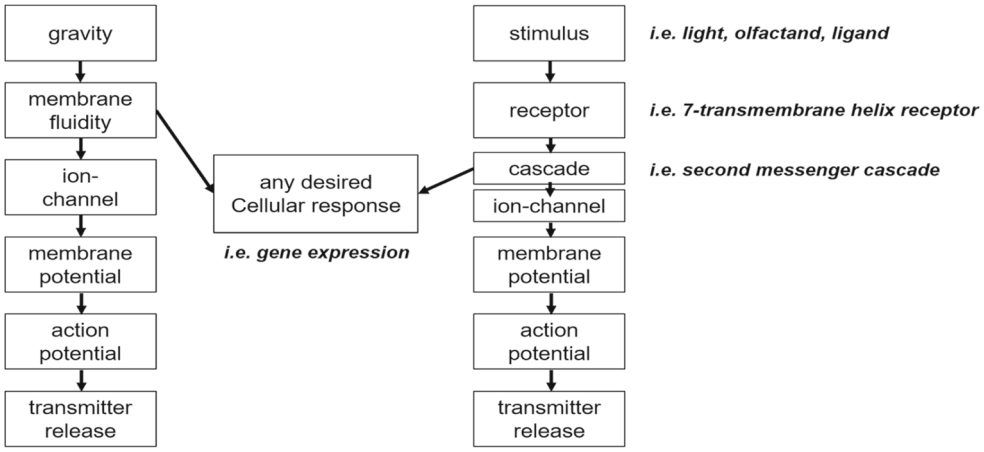

Fig. 1 Comparison of a classical sensory cascade, right side, with a restructured model of gravity perception, left side. Asides the effect of the input signal to ion-channels as given here as an example, second messenger cascades as well as membrane fluidity can induce a lot of other processes in cells as depicted in the scheme

Relevance for Biological Systems

At the end of this manuscript, we would like to discuss the more detailed consequences of our findings and statements above in terms of sensory physiology and their relevance for existing biological systems.

By sure some of the effects described in the text are small, and very often can be neglected in systems with defined gravity receptors. One example might be the 1–3% of reduction of action potential propagation speed under microgravity (Meissner and Hanke 2005). Having in mind that significant bigger changes are occurring normally, this might be ignored under normal conditions. However, the effects of membrane fluidity on ion channel open state probability for example are significant, and thus possibly cannot be ignored. Especially in cells having no specific gravity perceiving structure, fluidity effects might induce significant effects on the system level. This is especially due for the CNS. In principle, there is no need of the CNS to directly respond to gravity as there are sufficient inputs from sensory systems, but due to the described findings, it will do so, and this will have consequences up to the mental performance of astronauts.

According to the above said we do not argue:

does the system need this additional input?
but,
this input is given, so what are the consequences!

At this point is useful for better understanding, to additionally restructure the described findings in form of a sensory cascade, which can be compared to the standard structure for sensory systems as described in textbooks. This is done in the following scheme. It is assumed at the place of the signal input that any stimulus is received by a proper membrane integral receptor protein in a sensory cell (but also in any other cell i.e. neuron) by a small input of energy. From there it is propagated, processed, and used to create any desired reaction.

We now will take a closer look at the starting point, the sensory cell with the membrane-integrated receptor. In the following figure a scheme is given telling, how gravity perception of single cells could be fitted into the classical approach to sensory systems or any cell having receptor proteins i.e. for neurotransmitters (Fig. 1).

In this interpretation, the membrane fluidity, a physical parameter of any membrane, just replaces the classical membrane receptor. A second messenger cascade is not necessary, as ion channels and (any other membrane protein) are directly affected by the receptor. This is comparable in some aspects for example to mechano-sensing and other sensory channels. Additionally, by changes in membrane fluidity or due a second messenger cascade a variety of other processes can be induced in cells.

What finally remains to be asked is the question of the energy input, a question sometimes ignored in sensory physiology. The only and best interpretation possible here is that the interaction of membrane fluidity with gravity is thermodynamically driven. A prediction from our discussion thus would be that under microgravity a small temperature drop should be measured at the membranes. Most probably, this will not be easy to confirm because the effect must be small and that the systems usually are working against a big thermal background capacity.

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