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1 author:

Ludwig Edelmann
Universität des Saarlandes
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DOUBTS ABOUT THE SODIUM-POTASSIUM PUMP ARE NOT PERMISSIBLE IN MODERN BIOSCIENCE

L. EDELMANN

Anatomie und Zellbiologie, Universität des Saarlandes, 66421 Homburg/Saar, Germany
E-mail: ludwig.edelmann@uniklinikum-saarland.de

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Abstract - The sodium-potassium pump – the central molecular model of the generally accepted membrane pump theory (MPT) – is a misconception, according to the alternative association-induction hypothesis (AIH) of Gilbert Ling. With a discreet fraud coupled with the practice of appraising scientific publications and grant proposals by the peer-review system, the academic establishment – inadvertently or not – hinders a general discussion and acceptance of decisive arguments of the AIH. As a result, important discoveries over many decades, as well as new ways of basic research promising success remain largely unknown. The habit of funding safe research on ideas that have a false premise persists, and the wrong theory gets ever deeper entrenched. Science suffers.

Key words: Association induction hypothesis, cell water, ion association, membrane pump theory, Na/K-ATPase, paradigm change, peer review system, scientific fraud, sodium potassium pump

INTRODUCTION

It is quite unknown in modern biosciences to see change in many of its paradigms. Take as an example one of the central molecular biological models, that of the generally accepted membrane pump theory (MPT) – the sodium-potassium pump. This is a misconception according to the alternative association-induction hypothesis (AIH) of Gilbert Ling, the inventor of the microelectrode (12,21). Using this example, we can see how the entrenchment of a flawed hypothesis can often become a major impediment to the scientific advance through the introduction of fresher and better concepts.

RESEARCH AND THE ADVANCEMENT OF OUR "KNOWLEDGE" BASE

The scientific method of research into natural phenomena can be sketched as follows: the observation of certain phenomena leads to the formulation of theoretical models explaining the phenomena as logically as modern conceptual knowledge permits. Verifying or falsifying theoretical predictions derived from them in appropriate experiments tests the models. Only when the theoretical predictions of a model match all the observations completely can one assume that a phenomenon has been *understood* by science at least at some level of inspection, often only superficially at first. Thus, although scientific research is nearly always based on a paradigm or a hypothetic model, scientists are not always aware of the possibility of the model being wrong. Most scientific results are new observations that are explained plausibly within a given paradigm. Grants are awarded that sustain the arguments proposed in the application, not destroy them. Negative results are disparaged; even though they may tellingly do what Karl Popper proposed, indicate the untenable nature of the underlying hypothesis through that *nasty little fact that will not "fit" with the construct being promulgated.* Consideration of plausibility does not necessarily bring advancement of knowledge. Nevertheless, these new observations are not employed to test the paradigm at its basis, because the scientists are by that time usually convinced of its fundamental truth. Therefore, interpretations derived from an alternative new paradigm are not even considered and the new paradigm is rejected *a priori* without further testing. This "overvaluation" of existing paradigms prevents a critical discussion of new ideas that could help solving complex problems.

Abbreviations: **AIH**: association induction hypothesis; **Na**: sodium; **K**: potassium; **MPT**: membrane pump theory; **ATP**: adenosinetriphosphate; **ATPase**: adenosinetriphosphatase

ALTERNATIVE PARADIGMS AND THE CONTROVERSIAL SUBJECT OF THE SODIUM-POTASSIUM PUMP

Textbooks for biosciences describe the basic functions of living cells with the help of the so-called membrane-pump theory (MPT). This is a logic construct that arose as a result of experiments in the first half of the last century. We are led to assume that cellular water – the main ingredient of living cells – is prevailingly ordinary free water, in which potassium ions, the main cations of living cells, are freely dissolved. Sodium-potassium pumps in the cellular membrane provide for sodium ions to be actively (i.e. *through the consumption of energy*) pumped out of the cell against an electrochemical gradient and for potassium ions to be actively transported into the cell. A permanent and continuously operating active transport is necessary, because the membrane of the cell is open for a persistent movement of ions to the place of lower concentration. This model is used to explain the observation of an asymmetric distribution of chemically similar ions between a cell (a lot of potassium, little sodium) and surrounding medium (a lot of sodium, little potassium).

The existence of sodium-potassium pumps in the outer membranes of living cells has to be seen today as one of the central dogmas of biosciences. It is central because cellular structural principles and basic functions, e.g. regulation of the volume of the cell, modulation of electric potentials and transport of substances, cannot be understood, according to MPT, without these pumps.

It is a commonly unknown fact that there is, in addition to MPT, an alternative theory based on statistical mechanics, the *association-induction hypothesis (*AIH*)*, which explains the basic functions of living cells without the assumption of sodium-potassium pumps. The necessity for an alternative point of view resulted from the finding that under defined experimental conditions living cells do not provide enough energy accounting for the results when measuring the performance of the sodium-potassium pump. Because of thermodynamic reasons, there can be no pump. This falsification of the basic tenet of the MPT has not been disproved to this very day (19,22-24).

The basic difference between MPT and AIH must be seen in their quite disparate interpretation of cellular phenomena. While MPT explains physiological phenomena with features of the membrane, AIH ascribes physiologic functions to molecular interactions between the main parts of the *whole cell*, i.e. between proteins and water on the one hand and free ions on the other hand. The living cell is seen as a coherent dynamic protein-water-ion system of a high order. According to this theory the bulk of cellular water is not, as in MPT, free water, but water whose structure has been modified by interaction with cellular macromolecules. It is postulated that the distribution of charges in certain cellular proteins leads to a dynamic order of the polar water molecules so that this water accommodates sodium ions and many other substances differently from ordinary free water (13). Additionally, it is postulated that free ions can be selectively adsorbed to cellular proteins (*association*), where on theoretical grounds, potassium ions are preferred to sodium ions. Dynamic changes of inductively connected cellular proteins (*induction*) can lead to fast local changes of the very labile structure of water and of selective ion-association. These postulations lead to the deduction of theoretical equations with physically defined parameters for the description of transport of substances, asymmetrical distribution of ions, regulation of the volume of cells and electric potentials. These equations were successfully verified in the second half of the last century (17). An important part of AIH is its interpretation of biological work performance. The resting state of the cell is a metastable state of high potential energy, maintained in part by interaction with cardinal adsorbents like ATP. Work is done when the cell or one of its parts is triggered to drop to a lower energy state. One way to do this is to remove ATP, and one way to remove ATP is to hydrolyse it. It is the adsorption of ATP, not its hydrolysis – as assumed in MPT – that characterises its energetic function (16).

As already stated, AIH is largely unknown - despite the fact that it provides, unlike MPT, a unifying description of basic cellular functions and despite the fact that important experiments have falsified basic assumptions of MPT, at the same time precisely verifying predictions of AIH (17).

Given these facts, anybody looking at the issue from outside would ask for the reasons for the lack of acceptance of the AIH. Should the views and findings of AIH supporters be so devious that it is worthless to consider a new point of view and thus new ways of research? *Or is the literature that obscure with regard to these ideas that it has either not been read or has been dismissively treated (essentially ignored).*

Within the logic of MPT, AIH has to be refuted because it rejects the proven existence of the sodium-potassium pump. The proof of existence is done as follows: the activity of an enzyme (Na/K-ATPase) can be inhibited with a poison (ouabain). The enzyme can be found in the membrane of the cell. If a living cell is exposed to ouabain, an equalisation of the different potassium and sodium concentrations on both sides of the cellular membrane should occur in direct proportion in time to the leakiness of the membrane. The active transport of sodium and potassium is obviously inhibited by ouabain. Thus, the enzyme is the pump and its existence can be demonstrated with the poison (32). The result is that every theory, which rejects the pump, is necessarily false.

It has to be emphasised that the ouabain experiments are not questioned or ignored in the AIH. Rather, alternative

interpretations have been given ascribing an effect of ouabain not only on the membrane-situated Na/K-ATPase but also on intracellular proteins (18). A careful analysis of published results shows that it is not justified to call the Na/K-ATPase a pump (5,24,29). *Note that the active transport of ions across bifacial cell systems as e.g. different epithelia or frog skin has not been disputed, rather, models explaining this active transport have been published* (15).

However, after the decision to equate pump and Na/K-ATPase [with a Nobel Prize being awarded in 1997 to Jens Skou (33)], our science-system has put to work a discreet fraud to blight any general discussion of an alternative interpretation of the described experiments as well as of the physiological basic functions of living cells (25). This discreet fraud will be described below. Awarding Nobel Prizes becomes an act of canonizing ideas and hypotheses into fully-fledged sacrosanct theories.

THE DISCREET FRAUD AND ITS RESULTS

According to Charles Babbage (1), there are three kinds of scientific fraud:

•*Trimming* (levelling out of irregularities)
•*Cooking* (quoting of results fitting a theory while leaving out results contradicting it)
•*Forging* (inventing results).

(A fourth kind of fraud, *Hoaxing*, was mentioned by Babbage. It is not relevant here as the deceit of Hoaxing is intended to last for a time, and then be discovered, to the ridicule of those who have credited it).

While *Trimming* and *Forging* – as soon as they have been uncovered – can easily be recognised as frauds by everybody and be brand-marked as immoral, this is not true for *Cooking*. To the contrary, this form of fraud is universally employed as a legitimate means of enforcing favourite opinions. Given the complexity of biologic questions and given the increasing explosion of data and literature, practically every scientist has to rely on summaries, reviews and textbooks to enable them to work in their particular field. Reviews, however, whose contents are then reproduced in condensed form in textbooks, are designed in such a way that they produce, on the basis of generally accepted theories, the best possible uniform image without contradictions. That means that the authors (scientists!) knowingly keep silent about all the results contradicting accepted "basic truths". In the best of all cases, they hint at peripheral problems that still need solving. But they keep secret that with a different point of view, these results can be understood in terms of the above-defined criterion.

CHEATING BY CONCEALMENT

As an example, take the generally acknowledged geocentric world view (at a given time), all the reasons proving that the earth is at the centre of the universe would be referenced in a review, epicycles of certain planets would not be mentioned at all, or, at the very best, as marginal problems. A heliocentric world-view – favoured by a (known) minority – which can easily explain these epicycles, would not show up in this review. According to Babbage, this would constitute an obvious fraud.

Let us draw a parallel to the above-mentioned question about the existence of the sodium-potassium pump. Extensive reviews about this pump have been released without mentioning published experiments that falsify the pump idea (26) and without acknowledging that phenomena attributed to the pump cannot only be explained without the assumption of an energy consuming pump, but that they can be predicted directly within the framework of AIH.

Experimental results, which could foster doubts about the truthfulness of MPT, are not only left out of many reviews, but they are also left out of more detailed textbooks of cellular biology. A typical example occurred at the beginning of the last century, when many scientists thought that cellular potassium is bound to proteins, preferentially in the A band of the striated muscle (30). During the course of many decades, many attempts have been made, employing different methods, to show potassium binding to cellular structures of the striated muscle (8) as well as to isolated proteins (3,11). No method leads to a confirmation of the assumption. These negative results and ideas about the osmotic behaviour of muscle cells (9,10) lead to the conclusion that potassium is freely dissolved in free cellular water. This then justifiable conclusion of the Nobel Laureate, A.V. Hill, has to be seen as the main pre-condition for the postulate and the general acceptance of the sodium-potassium pump idea.

Stimulated by predictions of AIH, new cryomethods for electron microscopy have been developed many decades later, which have provided evidence for a weak binding of potassium to certain muscle proteins including myosin in the A band of the striated muscle (4,6). These results are remarkable for the following reasons:

•1) They show that proteins of a living cell possess qualities different from those of the same proteins when they have been biochemically extracted from the cells and are examined in isolation.
•2) They affirm postulated predictions of AIH concerning interactions between cellular proteins and ions and between proteins and water (4).
•3) One can safely assume that the knowledge of these findings would have prevented a postulation of the sodium-potassium pump completely.

Unfortunately, these findings are not mentioned or acknowledged in today's textbooks.

One could argue now that despite these facts, some

scientists should show interest in the controversy between MPT and AIH, especially as information is at hand. Knowing the dynamics and the network of our academic system, however, a fast change of mind cannot be expected. On the one hand, it is often hard to see a direct relation between one's own research and the controversy, and on the other hand, people with their own heads are effectively cast out of our repressive academic system.

LATERAL THINKERS HAVE *NO CHANCE* IN OUR SCIENCE SYSTEM

The pressures scientists find themselves exposed to are a matter of common knowledge. The *leitmotiv* is "Publish or Perish". Publications in renowned journals with a high "impact factor" are decisive for receiving grants and for one's career. Censors (experts called "peers") decide on the acceptance and rejection of grants and publications. Mistakes made by those anonymous peers are not legally challengeable or reversible (corrigible). The introduction of a peer-review system into science has its merits if a well-defined problem is to be worked upon effectively. In its current form the peer-review system, however, is utterly useless to evaluate revolutionary ideas (2,27). *A discovery by its very definition is something that is revealed quite unexpectedly.* Since the chances of receiving grants are very small, anyway, applicants have to rely on strategies that look something like this:

•1) The problem at stake should belong to an issue generally *en vogue*, i.e. the works belonging to the most recent quotation-monopolies - which can be taken from journals with a high impact factor - must form the basis of the research.

•2) The application should be formulated in such a way that the views of the possible reviewers are not questioned.

•3) One must not doubt at all established points of view, which might have been cemented as irrevocable truths by Nobel Laureates, because this prevents a favourable majority vote about the issue within the referees' committee.

This opportunistic approach does contradict the ethic basic rules for the scientific quest for the truth, but they are exactly what the money-giving institutes insist on [National Institute of Health, USA: "... the author of a project proposal must learn all he can about those who will read his proposal and keep those readers constantly in mind as he writes..." (28)]. The results of such an opportunistic behaviour are obvious: in its last consequence, the peer-review system with its rules is more effective in fighting ingenious ideas and revolutionary developments than the mediaeval church has ever been in their fight against inappropriate views.

To sum up: it has to be stated that the obviously legalised fraud of *Cooking* and the pressures of our academic system have mostly hindered consideration and acceptance of verified tenets of AIH during the past forty years.

NEW WAYS OF BASIC RESEARCH

By suppressing AIH and its justifiable criticism of MPT, science is doing harm to itself, because in doing so it bars new ways of basic research promising success. The situation can be described aptly with a well-known joke of Nasreddin Hodja, the famous national Turkish character:
In the light of a street-lamp, Hodja is looking for his lost key. When asked whether it was here that he has lost the key, he answers: "No, it was in the cellar." – "But why are you looking here?" – "You thickhead, how should I look in the cellar. It is dark there".

Obsessed with the overvalued idea that the solution to a scientific problem (key) is to be found within the framework of the accepted paradigm (street-lamp), an alternative paradigm is *a priori* rejected.

Opposing paradigms distinguish themselves by offering different solutions to a problem. Thus, a dispute about paradigms provides the chance to experimentally verify or falsify the alternative demands in new directions of research. Taking the above example of asymmetric distribution of sodium and potassium between cell and neighbouring medium, the opposing approaches and tests of MPT and AIH should be resumed:

According to MPT, an ion pump in the cellular membrane is responsible for the different concentrations of ions on both sides of the membrane. This postulate produces ways of research where the following questions are dealt with: Can the phenomenon observed be verified in isolated membrane-systems and in artificial membranes? What is the molecular mechanism of the postulated pump?

According to AIH, two mechanisms are responsible for the observed phenomenon: cellular proteins adsorb preferably potassium ions, if their life-specific structure is not disturbed as, e.g. after biochemical isolation procedures. Sodium ions show a lower solubility in cellular water and are thus partially excluded from the cell. These postulates produce approaches to research where the following questions can be dealt with: Can the phenomenon be proven with adequate methods? Which structure of cellular proteins is responsible for the option to adsorb ions selectively? Which structure of water is responsible for a low solubility of sodium? Can the phenomenon be examined using model systems?

The scientific results relating to the above-mentioned essential questions of MPT have to be classified as, at best, dissatisfying. Despite of years of attempts to show a net transport of potassium or sodium against an electro-chemic gradient, this could be achieved neither with artificial

membranes nor with isolated cellular membranes, and the molecular mechanism of a directed active transport has remained unaccounted for (5,24,29). However, the mechanisms postulated by AIH were verified using different independent methods, amongst others sliced muscle cells without a functioning membrane (14) and for the case of the water-problem also in model systems (20).

In today's state of the experimental verification of AIH, one has to conclude that a true understanding of cell-specific physical and biochemical processes is only possible if the structures of cellular proteins in the *living cell* and their molecular interactions with other proteins and with water and ions have really been understood. This leads to the demand to chose and develop non-destructive methods allowing determining *differences* in structure and properties between isolated systems of proteins and systems in the living cell. Emphasis should be placed on research of cellular water, concomitantly comparing the results with those of adequate aqueous model systems (31). It has to be stressed that not only new methods of research are wanted; what is needed for a true understanding of uncountable old and new results of research is, however, that alternative interpretations should be considered and tested.

Unfortunately, the rules of our academic system do not allow a public funding of the basic research suggested here, for as long as the deep subconscious belief in the sodium-potassium pump has not been shattered.

Note – A simplified German version of the present article has been published by *TELEPOLIS* (7)**.**

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