Medical Hypotheses 119 (2018) 98–101

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

A proposed tandem mechanism for memory storage in neurons involving magnetite and prions

Erik M. Alfsen[a], Fredrik C. Størmer[b], Arild Njå[c], Lars Walløe[c,*]

[a] Department of Mathematics, University of Oslo, Norway
[b] Norwegian Institute of Public Health, Oslo, Norway
[c] Division of Physiology, Institute of Basic Medical Sciences, University of Oslo, Norway

ARTICLE INFO

Keywords:
Memory storage
Magnetite
Prions

ABSTRACT

Knowledge about how information is stored in neurons of animals and in the human brain is still incomplete. A hypothesis related to long-term changes in synaptic efficiency has strong experimental support, but does not seem to be able to explain all observations. It has recently been proposed that magnetite together with a prion-like protein could be involved in a tandem mechanism for storage of memory in neurons in which electric impulses are received and reshaped by the magnetite to a form which can be accepted by the protein. The magnetite crystals can be magnetized by an electrical impulse, but they cannot hold the magnetism, which drops to zero after each impulse. Therefore, magnetite cannot be the substance in which information is stored. In the present paper we explain how a tandem mechanism could function in a neuron in which magnetite is situated together with a prion-like protein close to the cell surface membrane of the axon. We assume in addition that the information is stored in special *storage neurons*. With this, we propose a new hypothesis for information storage in neurons which could operate in addition to synaptic plasticity, but perhaps in different neurons.

Introduction

Knowledge of the mechanisms for storage of memory in neurons is incomplete. A hypothesis related to long-term changes in synaptic strength and the growth of new synaptic connections has strong experimental support [1]. A recent article [2] proposes the supplementary hypothesis that there are neurons in which a combination of magnetite and prion-like proteins (or prions for short) are involved in a tandem-mechanism in which the magnetite amplifies and reshapes electrical pulses to a form that can be accepted by the protein. An extension of this hypothesis is that there are special neurons in which this tandem-mechanism takes place. In this paper, we will discuss such an extended tandem-hypothesis and explain how we think a tandem-mechanism may function in such neurons. More specifically, an extension of this hypothesis is that there are neurons in which such proteins store the information, while the magnetite is needed to amplify electrical signals so that they can switch the protein between its two possible shapes, a ground state or initial condition, and a transformed state in which the neuron stores one bit of information. We will in this paper explain how we think the tandem-mechanism may function in neurons.

Prions have the crucial property that they can change shape from a normal resting form to an alternate chain-formed version. For brevity, we refer to a prion in the normal form as being in the *ground state*, and to one in the alternate form as being in the *excited state*. In [3] it is explained how a prion can be switched from the ground state to the excited state by an intricate *prion-chain reaction* triggered by an electric impulse.

It has also previously been proposed that magnetite is involved in the storage of information in neurons [4,5]. Magnetite is an iron oxide (Fe_3O_4) which is widely found in living organisms without being involved in any known biochemical reactions.

Electron microscopy has indicated the presence of a minimum of 5 million single-domain magnetite crystals per gram in human brain tissue. Black strings of aggregated particles can be extracted from brain tissue and can be viewed under low power through an optical dissecting microscope. The crystals range in size between 10 and 70 nm in diameter [6]. Magnetite crystals have also been found in bacteria and fish, where they were seen to be organized in membrane-bound chains with up to 80 single-domain crystals per chain [7,8]. Such chains appear to be present across all animal species.

The particles in these chains are magnetite crystals that are different from those formed through geological processes. The morphology of magnetite particles in living organisms is in fact particularly well suited for information storage in neurons because they have the crucial

* Corresponding author at: Division of Physiology, Institute of Basic Medical Sciences, University of Oslo, P.O. Box 1103, Blindern, NO-0317 Oslo, Norway.
E-mail address: lars.walloe@medisin.uio.no (L. Walløe).

https://doi.org/10.1016/j.mehy.2018.07.003
Received 11 February 2018; Received in revised form 1 June 2018; Accepted 2 July 2018

property that they can easily be magnetized by electrical impulses, but cannot hold the magnetism, which very quickly drops to zero after each impulse. Therefore, magnetite cannot be the substance in which information is stored. However, it is conceivable that information can nevertheless be stored in a neuron by means of a prion-chain reaction which switches prion in a neuron from the ground state to the excited state, whereby one bit of information will be stored in the neuron. In this process, electrical pulses driven by action potentials along a pathway of axons are magnetizing a chain of magnetite crystals. In this paper, we will present a version of the tandem hypothesis in which such a chain is located in the initial segment of an axon immediately downstream from where the action potential is generated.

However, it has recently been suggested that magnetite chains together with prions could be involved in a tandem mechanism in which incident electric impulses are received and reshaped by the magnetite, giving it a form that can be accepted by a prion in which the information can be permanently stored. This magnetite crystal should be located in the initial segment of the axon immediately downstream from where action potentials are generated,

In this paper we will explain how such a mechanism may function in a neuron where a nanocrystalline magnetite chain is located together with a prion close to the cell surface membrane, and how the electric impulses could trigger prion-chain reactions such that the information is stored in the prion.

A storage cell hypothesis

Nerve impulses (action potentials) are all-or-none electrical signals that encode neural information for long-distance communication along nerve fibers (axons). Action potentials have large, fixed amplitudes (about 100 mV), short durations (about 1 ms) and travel through long axons at speeds that range from below 1 to above 100 m s^{-1}, depending on the axon diameter and degree of myelination.

Action potentials are elicited if the membrane potential is depolarized to a threshold level. The threshold is lowest in the initial segment of the axon. After an action potential is generated at this site, it can spread without decay down the axon and all of its branches, and may (although with signal decay) also invade the cell body and proximal dendrites. Graded transmembrane potentials show exponential decay with distance from the generation site in the neuron, but multiple small potentials may summate so that the threshold is reached and an action potential is fired in the initial segment of the axon, even if each input is too small to reach the threshold alone.

The transmembrane ionic currents associated with the passage of a propagated action potential (an inward Na^+ current through voltage-gated sodium channels, and, after a brief delay, an outward K^+ current through voltage-gated potassium channels) will generate a local rotating current that could potentially magnetize a properly oriented rod of magnetite nanocrystals, as we explain here. We propose a tandem mechanism by which the propagation of an action potential in an axon could, given that specific conditions are satisfied, magnetize a local rod of magnetite nanocrystals that in turn could change the conformation of a local prion and store a permanent memory of the event.

How can electrical signals magnetize the magnetite chain?

According to the tandem hypothesis, information is stored in a special type of neurons, called *storage neurons*, which contain one and only one magnetite chain together with a prion that can be in one of two possible states.

In a storage neuron, the bursts of Na^+ ions into the cell and K^+ ions out of the cell create vortices that rotate on their axes like short-lived electrical currents. When such vortices rotate around a magnetite chain, they can magnetize it. These vortices arise when two oppositely directed flows of ions pass through neighboring membrane areas. If P1 and P2 are sufficiently close ion channels, the two flows will interact

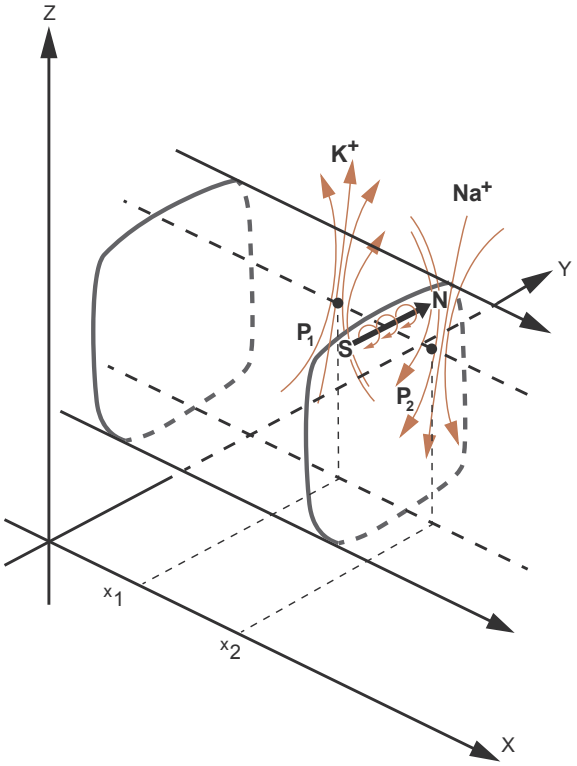

Fig. 1. Two oppositely directed bursts of ions through neighboring ion channels can create vortices that magnetize the magnetite chain in a storage neutron. The action potential travels along the cell surface membrane in the x-direction. The sodium channels are open near point P_2 and the potassium channels near point P_1. The magnetite chain S-N is located laterally close to the cell membrane and oriented in the y-direction.

and produce vortices that rotate clockwise in the (*x*-*z*)-plane (Fig. 1).

According to this argument, incident signals in a storage neuron can create vortices of short-lasting electrical currents that rotate like a whirlwind around the magnetite chain, and these currents can magnetize the chain. However, the magnetite chain differs from an electromagnet, as described below.

How can the magnetite chain change the shape of the prion?

We have seen that the magnetite chain in a storage neuron can be magnetized by currents rotating around it, but it is not so easy to explain how the magnetic chain can change the shape of the prion, since it requires an electric and not a magnetic impulse to do this. Here it may be helpful to use an analogy with a familiar electric device, a transformer, which sets up a pulsating electromagnetic field that produces eddy currents.

In the same way, when the magnetite chain of a storage neuron is magnetized by electric pulses, it will set up a pulsating electric field which produces ionic currents. These will rotate in right-handed vortices around the magnetized magnetite chain like a whirlwind. A detailed proof of this can be obtained by an elementary argument, but all we need to know here is that the electric field at a given point is largest close to the magnetized chain, and that it decreases rapidly with increasing distance from the chain.

Why is nanocrystalline magnetite particularly suited for the storage of information in neurons?

Magnetite (Fe_3O_4) is an iron oxide which differs from ordinary rust (Fe_2O_3) in its crystalline structure and its specific magnetic properties. In molecules of ordinary rust, all the innermost electronic shells are

filled, but in molecules of magnetite, there is one loosely bound electron outside the full innermost shells. The extraordinary magnetic properties of magnetite are largely due to this electron. The crystal structure of nanocrystalline magnetite in neurons differs from that of magnetite in geological deposits. Geological magnetite crystals are usually octahedral, whereas those of biological magnetite are cubo-octahedral [9]. The individual crystals in a magnetite chain are tiny magnets which are aligned "north pole to south pole" along the axis of the chain, each with its poles in the faces of the crystal lying perpendicular to the axis.

We know that magnetization of ferromagnetic substances involves crystal *domains*, each usually containing a large number of crystals, and that the magnetization process consists of a rotational displacement of these domains so that they are oriented in the direction of the magnetizing magnetic field [10].

The magnetite chain in a storage neuron cannot be magnetized by rotation of its single crystal domains since they are tiny magnets and are already oriented north pole to south pole along the chain axis. However, they can be magnetized by a quantum mechanical process. This is based on quantum mechanical resonance between a strong magnetizing exterior field and the weak magnetic fields of the crystals in the chain, which are forced to oscillate in the same quantum mechanical phase as the magnetizing field. The process is explained in more detail in [11] where the phases in question are related to the complex wave functions of quantum mechanics. Here we explain the idea in non-mathematical terms. For this purpose we will make use of the old quantum theory that the electrons in an atom rotate in orbits around the atomic nucleus. In this picture, the loosely bound electron in the magnetite molecule may be thought of as a particle rotating in orbit around a 'core' consisting of the atomic nuclei of iron and oxygen and the other tightly bound electrons.

When a storage neuron is in the resting state, the crystals in its magnetite chain are completely unrelated in phase. But when the chain is subject to a sufficiently strong exterior magnetic field, all crystals in the chain are forced to oscillate in the same phase as the exterior field. After this, the chain can no longer contain crystals in opposite phase whose magnetic fields erase each other. Therefore, the crystals are now all in the same phase as the magnetizing exterior field, and the chain is magnetized up to its greatest possible strength. The quantum mechanical equations in this process are explained in [11].

The magnetization of a magnetite chain by this process requires a certain critical energy level. If the critical energy level is exceeded, the chain will always be magnetized up to the same maximal strength. The critical energy level is here called the *magnetization energy* of the chain. Thus, no magnetization of the magnetite chain of a storage neuron will occur if it is subjected to energy levels below the magnetization energy, whereas any energy level above this magnetization energy will magnetize it up to its full strength but no further, however strong the signal is. This means that the magnetization process of the magnetite chain in a storage neuron is different from that of the iron core in an electromagnet, in which the magnetism increases proportionally with the strength of the magnetizing current.

Each domain in the nanocrystalline magnetite in neurons contains a single crystal. These crystals are of the same shape and size, and they also act as tiny magnets. When the magnetic chain of a storage neuron is magnetized up to its maximal strength, the magnetic energy of the chain is equal to the magnetic energy of a single crystal multiplied by the number of crystals in the chain. The magnetization energy of a magnetite chain therefore depends only on its length, i.e. on the number of crystals in the chain.

According to the tandem hypothesis, one bit of information is stored when the prion in a storage neuron is switched from the ground state to the excited state. This requires a certain amount of energy which must be provided by the magnetized magnetite chain. We call this energy the *excitation energy* of the prion.

In order to switch the prion from the ground state to the excited state, the incident signal must provide sufficient energy to magnetize the chain, and the chain must in turn provide enough energy to create "electrical whirlwinds" that can excite the prion. This means that the magnetization energy held by the magnetite chain, which depends on its length, must exceed the excitation energy of the prion. The necessary amount of energy can therefore only be provided by a magnetite chain of a certain length. The minimum chain length needed for excitation of the prion is here called the *critical chain length* for the magnetic chain in a given storage neuron.

A propagating action potential in the initial segment may stop if its ionic currents are attenuated. The action potential in the initial segment provides the magnetization energy of the chain and the excitation energy of the prion. The energy drain will be smaller if the prion is already in its excited state. Thus, propagation of the action potential beyond the initial segment will depend on the conformational state of the prion.

Discussion

How can the proposed tandem mechanism function in neurons?

It has been an open question whether memory storage takes place only in synapses or also in specialized neurons. Studies on axon initial segment plasticity are reviewed in [12]. We assume that both entities may be involved in the storage process. If information storage is based on the summation of a large number of local signals, the important entities are the synapses at which the incident signals are targeted. But this is not the case for information storage in storage neurons based on the proposed tandem mechanism. In this case, the most important entities are not the synapses but the initial segments of the axons of the post-synaptic neurons where action potentials are initiated and where magnetite chains are presumed to be located.

Here we discuss the propagating action potentials in a pathway of axons which terminates in a storage neuron. The magnetite chain in a storage neuron can be magnetized most efficiently if it is located laterally and near the cell surface membrane. We say that the storage neuron has a "threshold density of ion channels" if there are enough Na^+ and K^+ channels near the magnetite chain to release the rotating currents of ions that can magnetize the chain.

We argue, based on the quantum mechanical properties of nanocrystalline magnetite, that the *magnetization energy* of the magnetite chain depends only on the length of the chain, which must be above the *critical length* to provide the *excitation energy* needed to switch the prion in the cell from the ground state to the excited state.

The following three assumptions are required as part of the tandem hypothesis for memory storage by magnetite and prions:

A1. The magnetite chain in a storage neuron is located close to the cell surface membrane and is laterally oriented in the neuron.

A2. The density of ion channels in the storage neuron is above the threshold level.

A3. The length of the magnetite chain in the storage neuron is above the critical length.

Given these assumptions, the tandem hypothesis explains how a propagating signal can magnetize the magnetite chain in a storage neuron, which in turn switch the prion in the storage neuron to the excited state and thereby stores one bit of information.

When a signal in a pathway of axons arrives in a storage neuron, then there are two scenarios:

Case one: The prion is in the ground state. Then it is switched to the excited state in a process which is fed by the energy produced by a flow of cations through ion channels (sodium in—potassium out). We will here call this energy "the trigger energy". By A1 and A2 this trigger energy must exceed the excitation energy of the prion. But a subtle point in the tandem hypothesis is that the trigger energy must not be so large that there is energy left for the signal to continue along the axon and initiate an excitation in another neuron downstream. Therefore, the trigger energy must be bounded above as well as below: It must be larger than the excitation energy of the prion, but it must be less than

two times this excitation energy. If this requirement is satisfied, then this storage neuron will be storing one bit of information, namely the information that the signal has arrived here. But nothing will happen downstream.

Case two: The protein is in the excited state. Then no energy is needed to change the state of the protein, so the trigger energy will only be reduced with the energy needed to magnetize the magnetite chain, and this energy is much smaller than the excitation energy of the prion. (The magnetization of the magnetite chain is a quantum mechanical process which needs an insignificant amount of energy in comparison with the chemical energy needed for the excitation of the prion, as explained in [11].) Therefore the signal may continue downstream.

Conclusions

According to the tandem hypothesis, the storage neurons must satisfy three assumptions. The first of these specifies the location of the magnetite chain in the cell, the second requires a sufficient number of Na^+ and K^+ ion channels near the magnetite chain to permit the ion bursts that magnetize the chain, and the third requires the magnetite chain to be long enough to provide sufficient energy to switch the prion to the excited state and store information in the cell.

If cells are to function as storage neurons, it must also be possible to retrieve stored information when needed, through processes that are dependent on whether the prion is in the excited state or the ground state. It is conceivable that such retrieval of information could be achieved by sending a test signal into the cell via an appropriate synaptic connection.

Conflict of interest

None.

Funding

The research is funded by the two university departments.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.mehy.2018.07.003.

References

[1] Kandel ER. The molecular biology of memory storage: a dialogue between genes and synapses. Science 2001;294:1030–8.
[2] Størmer FC, Alfsen EM. Is a combination of magnetite and prions involved in the memory storage in the human brain? Med Hypotheses 2015;85:111.
[3] Si K, Kandel ER. The role of functional prion proteins in the persistence of memory. Cold Spring Harb Perspect Biol. 2016;8:a021774.
[4] Størmer FC, Laane CMM. Membrane-bound memory in the neurons? Med Hypotheses 2009;73:462.
[5] Banaclocha MAM, Bókkon I, Banaclocha HM. Long term memory in brain magnetite. Med Hypotheses 2010;74:254–7.
[6] Kirschvink JL, Kobayashi-Kirschvink A, Woodford BJ. Magnetite biomineralization in the human brain. Proc Natl Acad Sci USA 1992;89:7683–7.
[7] Kirschvink JL, Walker MM, Chang S-B, Dizon AE, et al. Chains of single-domain magnetite particles in chinook salmon, *Oncorhynchus tshawytscha*. J Comp Physiol 1985;157:375–81.
[8] Kirschvink JL, Walker MM, Diebel CE. Magnetite-based magnetoreception. Curr Opin Neurobiol 2001;11:462–7.
[9] Mann S, Sparks NHC, Walker MM, Kirschvink JL. Ultrastructure, morphology and organization of biogenic magnetite from sockeye salmon, *Oncorhynchus nerka*: implications for magnetoreception. J Exp Biol 1988;140:35–49.
[10] Harnwell GP. Principles of Electricity and Magnetism. McGraw-Hill; 1949. Chap. 11, Sec. 11.6.
[11] Alfsen EM. A note on magnetization of magnetite chains in neurons. Supplemental Materials.
[12] Grubb MS, Shu Y, Kuba H, Rasband MN, et al. Short- and long-term plasticity at the axon initial segment. J Neurosci 2011;31:16049–55.