Activitas Nervosa Superior Rediviva Volume 63 No. 1 2021

HYPOTHESIS

Heart memory or can transplanted heart manipulate recipient´s brain control over mind body interactions?

Ján Lakota [1,2], Fedor Jagla [1], Oľga Pecháňová [1]

[1] Centre of Experimental Medicine, Slovak Academy of Sciences, Institute of Normal and Pathological Physiology, Bratislava, Slovakia, [2] Faculty of Management, Comenius University, Bratislava, Slovakia.

Correspondence to: Jan Lakota, MD, PhD, Centre of Experimental Medicine, Slovak Academy of Sciences, Institute of Normal and Pathological Physiology, Sienkiewiczova 1, 813 71 Bratislava, Slovakia
e-mail: jan.lakota@savba.sk

Submitted: 2021-05-08 Accepted: 2021-05-17 Published online: 2021-05-17

Key words: **heart; brain; memory transfer; exosomes**

Act Nerv Super Rediviva 2021; **63**(1): 49–51 ANSR63121H01

Abstract

Here we present a hypothetical explanation of the donor "heart memory transfer" in patients after heart transplantation. The donor heart can accumulate the memory engrams which are formed in the brain of the donor and hypothetically retransfers it to the brain of the recipient in the form of exosomes. The support comes from data obtained from a small albeit statistically not disregarded group of patients.

Main

The heart is the very first organ that does function in prenatal development of a person even when the brain is not yet developed. If we assume the memory as a property of very diverse biological systems we must admit the fact that even the heart can have a memory (Rosen *et al.* 2003). Very early prenatally the fetal heart has to react to changes in the circulation system of the mother. The gravidity is in fact a state very sensitive to various bio-psycho-social conditions and the fetal heart has to store the information how to react in several situations in order not to harm development. Postnatally, the heart and the brain communicate as a two-way communication system and they cannot exist without each other. Brain accepts the signals from the heart which can influence the behaviour of a given person. On the other hand, the brain can affect the signals sent by the heart and with some exaggeration to say that the brain can pre-argument the voice of the heart to the voice of reason (McCraty 2015). Therefore, the scientifically important question is also whether the transplanted heart may influence the behaviour of a recipient´s person and to say that the heart can pre-arguments the voice of reason to voice of heart. Especially, having in mind that the heart emerges as a critical component of the emotional system (McCraty 2015).

In searching for the basis of the memory explanation we are up to date coming to the same fundamental problems: How are the memories formed, stored, how long can they last, and how are they recalled/retrieved? Moreover, an increasing number of data (Bunzel *et al.* 1992; Pearsall *et al.* 2000; Liester 2020; Tan *et al.* 2020) suggests that memories can be stored in the heart and recalled/retrieved from this organ.

Let's recall three (6%) patients from the study of Bunzel et al (1992). Patient 1: "The new heart has changed me. One could say, well, not exactly, but one might put it like that: the person whose heart I got was a calm person, not hectic, and his feelings have been passed on to me now." Patient 2: "I love to put on earphones and play loud music, something I never did before. A different car, a good stereo-those are my dreams now. And I have thoughts now that I never had before." (remark patient: 45 year old man, donor

17 year old boy)." Patient 3: "… actually my wife and I, we could get married in church now. Because I'm no longer the one she originally married. I'll write to the Pope. . ."

By careful analysis of these three patients one can see that the change of the recipient after heart transplantation is based on feelings, perceptions and apprehensions. The recipients didn't learn new melodies, new abilities and new knowledge. What has been changed was the embedded personality trait.

Heart transplantation (HTx) surgically interrupts the parasympathetic vagal neurons and the intrinsic postganglionic sympathetic nerve fibers to the myocardium (Awad *et al.* 2016). It should be noted that all these patients were interviewed about 3 months after surgery (Bunzel *et al.* 1992) i.e. before any heart reinnervation could occur (sympathetic reinnervation occurs at least 5 to 6 months after HTx, parasympathetic reinnervation seems to occur more than 1 to 3 years following HTx (Awad *et al.* 2016).

The history of memory transfer is rich in data observed in lower species. The "memory transfer hypothesis" in planarian worms by McConnell (McConnell 1979) finally showed that RNA could be the substrate of the memories. The McConnell hypothesis has been rejuvenated in 2013 by Levin (Shomrat & Levin 2013). Recently, in the experiments on sea snail *Aplysia californica* the Glanzman's group successfully transferred memory by introducing RNA extracted from the nervous system of a trained snail into a naïve recipient (Bédécarrats *et al.* 2018). Moreover, RNA extracted from trained snails was able to induce long-term sensitization in vitro only in sensory and not in motor neurons. All above mentioned authors used the "naked" extracted RNA to successfully transfer memory into a naive recipient. The RNA spectrum in the extracted RNA can vary – from messenger RNA, ribosomal RNA and a still growing pleiad of non-coding RNAs (RNA-Based Regulation 2020). So far the situation seems more perplexing than one could expect. It has been stated by the authors: This observation offers dramatic support for the idea that memory can be stored nonsynaptically and indicates the limitations of the synaptic plasticity model of LTM storage" (Bédécarrats *et al.* 2018). What the authors did not –they did not extract exosomes. They extracted the RNA from whole pleural-pedal and abdominal ganglia. In other words the cellular/extracellular RNA localization has been missed.

In case of transplanted, for a couple of months "denervated", heart one can ask a question: How is it possible to observe such phenomenon of heart memory transfer (at least in 6% patients) as described in Bunzel *et al.* (1992). The straightforward possible answer is: Through the extracellular vesicles (EVs), mainly exosomes. Exosomes are a subset of EVs, with an average diameter of approximately 30-150 nanometers (for review see Kalluri & LeBleu 2020). Exosomes as the vehicles of RNA memory transfer have been described earlier (Liester 2020), however, among dozens of other possibilities.

A diversity of cells including neurons, epithelial cells, mast cells, cells of the immune system have been demonstrated to have the ability to produce and secrete exosomes. Moreover, "free" exosomes are present in blood and other bodily fluids (cerebrospinal fluid, saliva, sputum, urine) (Keller *et al.* 2011). Exosomes consist of a lipid bilayer membrane and they lack cellular organelles. They contain a broad spectrum of biomolecules: DNA fragments, mRNA, miRNA, lipids, proteins, small signalling peptides (Smalheiser 2007). Exosomes can cross/are crossing the blood brain barrier (Banks *et al.* 2020). According to the three models the exosomes i) directly fuse with the cell membranes, ii) are absorbed into the cells by active endocytosis or iii) their binding and their uptake are mediated via specific receptor protein(s) present on the surface of the target cell(s) (Hagiwara *et al.* 2014). Moreover, several proteins that are expressed near the postsynaptic membrane, and that regulate synaptic plasticity, are other leading candidates to be carried as cargoes by postsynaptic exosomes. A variety of transcription factors, including cAMP response element-binding protein (CREB), are known to be expressed locally in dendrites and undergo induced mobilization in response to synaptic activity. CREB has a well-documented role in neuronal plasticity and long-term memory formation in the brain and has been shown to be integral in the formation of spatial memory (Silva *et al.* 1998; Chauhan *et al.* 2020). Although current thinking is that such transcription factors translocate to the cell body, the chance that they became an exosome cargo (Smalheiser 2007) is plausible.

This hypothesis makes at least some features of the heart physiology of memory rather simple. The memory is created mainly in the brain. It is transferred to the heart and vice versa by exosomes. This occurs dynamically, during whole human life. The neural paths do not play any or, only minimal role. Nevertheless, this doesn't exclude the memory is created in the heart too. This idea is rather marginal, although not entirely excluded. As stated above, the exosome memory transfer could be a possible explanation in the personality changes of heart transplant recipients. Moreover, in a small cohort study the authors (Broccolo 2018) claim that: "This study shows that patients might feel that transfusions could modify their behaviour or values and that certain personality traits of the donor could be transmitted".

All of these observations are in concert with the proposed hypothesis of the "exosome memory transfer" in the heart transplant recipients. They support the idea that at least a part of human memory is stored in the heart and temporally circulates in blood vessels. Finally it dynamically interacts with all organs, mainly the heart and the brain. This concept is now open for experimental testing.

Conflicts of interest

There are no conflicts of interest.

Acknowledgments

This work has been supported by the Foundation for Cell transplantation.

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