CONFIDENTIAL

The cellular basis of feelings and its medical implications

A Research Proposal

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1. Feelings: biological origins and medical impact

Feelings are the mental experiences that accompany and describe a particular class of ongoing body states. The physiological states eliciting feelings are of two main types: drives (hunger, thirst, pleasure, pain, etc.) and emotions (fear, sadness, joy, etc.). Feelings provide a high level of homeostatic regulation, since conscious experience forces attention on the underlying physiological conditions, and thus facilitates responses to and learning from both adverse and advantageous situations. In turn, such learning permits the anticipation of future situations and the planning of suitable behaviors, thus conferring an important evolutionary advantage on the organisms that possess them.

The biological relevance of feelings is illustrated by the fact that their dysregulation underlies some of the most devastating medical and public health problems of our time — for example, depression, substance addictions and intractable pain, which are all disorders centered on pathologies of feeling. Depression alone is the leading cause of disease in the US and the leading cause of non-infectious disease worldwide.

Despite the magnitude of these issues, the neurophysiology of feelings remains largely mysterious, and the mechanism of the aforementioned pathologies has yet to be fully understood. Consequently, the available therapies for these disorders are not specific and are unsatisfactory. Elucidating the cellular basis of feeling is likely to lead to new therapeutic advances and have major biomedical impact.

Unlike any other life form before them, the first organisms capable of conscious experience became aware of aspects of their own existence. Feelings paved the way for higher levels of cognition, culminating in the modern human mind. Feelings constitute the most rudimentary level of consciousness and the foundation on which its more complex levels are erected. Shedding light on the physiology of feelings will therefore significantly advance our understanding of the human mind.

2. The cellular basis of feelings

We hypothesize that feelings emerge from cellular processes that take place in the unmyelinated axons of the interoceptive nervous system.

Three lines of evidence lend support to this hypothesis, the outline of which has just been published in *Nature Reviews Neuroscience*[1], one of the journals with the highest citation impact within neuroscience.

First, feelings pertain to the physiological state of the body. Feelings describe states of the body, in particular visceral sensations, and provide an experiential window into homeostatic processes.

Second, several areas of the nervous system that receive interoceptive signals (i.e. signals pertaining to the physiological state of the body), and that together monitor the internal milieu and act as a central homeostatic “control panel”, are activated when feelings are induced.

Third, interoceptive pathways and centers are predominantly unmyelinated, that is, their axons lack the glial cell wrappings known to accelerate nerve conduction.

We posit that this lack of myelin is critical to the cellular processes leading to the emergence of feeling states. Specifically, we venture that the absence of myelin around interoceptive neurons allows membrane receptors on the surface of these cells to be reached by circulating ligands (Fig. 1), a process that plays a central role in the sensing of the internal milieu and consequently underlies interoception.

This scenario would provide an explanation for the persistence of unmyelinated fibers in higher animals and provide a pivotal insight into the cellular basis of feeling and consciousness.

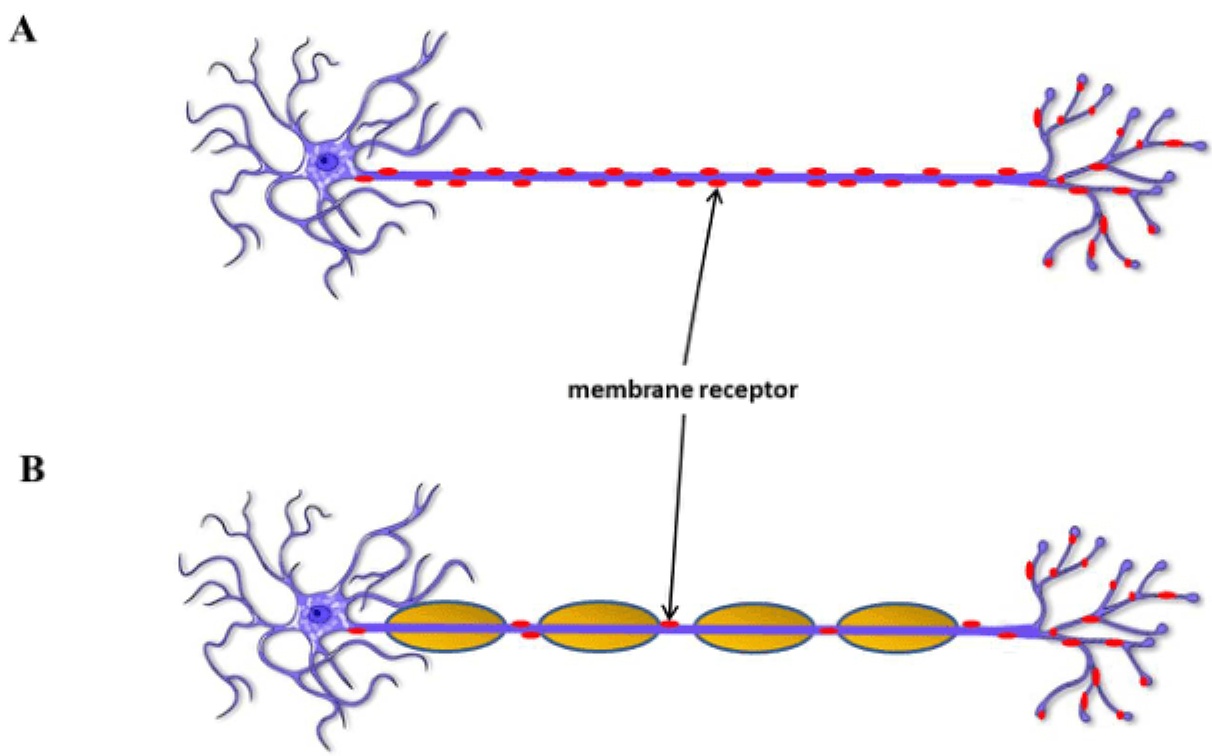

Figure 1. In unmyelinated axons (A), membrane receptors present along the length of the fiber are exposed and free to interact with circulating ligands. In myelinated fibers (B), on the other hand, the myelin sheath blocks ligand access to membrane receptors, limiting the chemosensitivity of the axonal trunks.

3. Preliminary experimental approach

A. We will test the hypothesis that myelin blocks the access of circulating ligands to membrane receptors. The first proof of principle set of experiments will be conducted in vitro.

Several membrane receptors involved in interoception are known to be expressed in the axonal trunk (i.e. the length of the axon, as opposed to its terminals) of interoceptive neurons, including the vagus nerve. Moreover, binding of ligands to these receptors can trigger action potentials, showing that they are indeed functional.

We will study the function of these receptors in cultured neurons, both in the presence and absence of myelin sheaths. If myelin indeed impairs ligand binding, one would expect that unmyelinated fibers would be responsive to the ligand treatment, whereas myelinated ones would not.

Artificially induced myelination might interfere with axonal function non-specifically. To rule out this trivial explanation, we will apply ligands to either the nerve terminals alone, or the axonal trunk alone. If myelination hinders receptor activation by physically blocking ligand access, ligands should have no effect in the axonal trunk of myelinated fibers, while retaining their effect in axonal terminals. On the other hand, if the myelination process interferes with fiber function non-specifically, the effect of ligands should be diminished both in the trunk and the nerve terminals.

B. The next phase of this project will proceed in an in vivo model. Myelination of normally unmyelinated neurons can be induced via expression of a specific membrane protein, neuregulin 1 type III (NRG1-III). We will create mutant mice in which different subsets of interoceptive fibers have been myelinated. The function of these fibers will be tested upon treatment with the respective ligands. Fiber activity can be monitored with the help of electrophysiology and/or imaging techniques. We will also study the behavior of these animals. Tissue damage leads to the release of circulating molecules that bind interoceptive receptors, triggering pain and several accompanying measurable behaviors. Monitoring these pain-associated behaviors after ligand treatment in animals bearing abnormally myelinated interoceptive neurons, will address the physiological role of myelin sheaths and test our hypothesis that myelin impairs ligand binding and interoceptive function.

C. In a subsequent phase, motivational and emotional correlates (assayed via tasks related to motivation, emotion and reward) will be studied in existing animal models of hyper- and undermyelination.

D. A complementary approach involves using currently available pharmacological agonists and antagonists of interoceptive membrane receptors. We will test the effect of these molecules on animal models of depression and other disorders of affect. Given that these are primarily pathologies of feeling, affecting body state sensing by modulating the function of interoceptive fibers pharmacologically may influence the general affective state of the animal as inferred by its behavior.

Further reading

1. The nature of feelings: evolutionary and neurobiological origins. Damasio A, Carvalho GB, **Nat Rev Neurosci**. 2013; 14(2):143-52.