Journal of Physiology - Paris 96 (2002) 251–255

Journal of
Physiology
Paris

www.elsevier.com/locate/jphysparis

The Astrocentric Hypothesis: proposed role of astrocytes in consciousness and memory formation

James M. Robertson*

2849 Zeeland Avenue, Baton Rouge, LA 70808, USA

Abstract

Consciousness is self-awareness. This process is closely associated with attention and working memory, a special form of short-term memory, which is vital when solving explicit task. Edelman has equated consciousness as the "remembered present" to highlight the importance of this form of memory (G.M. Edelman, *Bright Air*, *Brilliant Fire*, Basic Books, New York, 1992). The majority of other memories are recollections of past events that are encoded, stored, and brought back into consciousness if appropriate for solving new problems. Encoding prior experiences into memories is based on the salience of each event (A.R. Damasio, *Descartes' Error*, G.P. Putnam's Sons, New York, 1994; G.M. Edelman, *Bright Air*, *Brilliant Fire*, Basic Books, New York, 1992). It is proposed that protoplasmic astrocytes bind attended sensory information into consciousness and store encoded memories. This conclusion is supported by research conducted by gliobiologist over the past 15 years.
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Keywords: Consciousness; Memory formation; Information processing; Gap junctions; Calcium waves

1. Introduction

Consciousness is the sense of an individual self that interacts with an ever-changing external and internal environment. The mechanism underlying this phenomenon is unknown.

The major obstacle to determine the neurological basis of consciousness is that research on perception has increasingly demonstrated that the brain does not process sensory information in a unified manner, but that such information is continuously subdivided or parcelated [51]. An anatomical region that integrates this parcelated sensory information into a unified whole has not been identified. This paradox was first described over a century ago [24] and is generally referred to as the binding problem [9].

It is proposed that there is an anatomical entity that binds parcelated sensory information in a unified manner. Protoplasmic astrocytes in the cerebral cortex have the necessary physical, chemical and structural elements to integrate sensory information. Furthermore, as described below in detail, research supports the contention that these cells have the ability to display (consciousness) and store (memories) this information.

2. Sensory binding

2.1. The Astrocentric Hypothesis

Protoplasmic astrocytes receive a copy of sensory information that is transferred from presynaptic to postsynaptic neurons at the synapse that all three share. Integration (binding) of information occurs with the conversion of astrocytic intracellular calcium $[Ca^{2+}]_i$ into intercellular oscillatory calcium waves that are synchronized as they travel via gap junctions throughout the functional syncytium formed by these structures [26].

Two additional pathways for autocrine propagation of astrocytic calcium waves utilizing ATP and glutamate have been identified [5,18,19,20]. The three pathways are interconnected and synergistic.

ATP stimulates calcium-dependent release of astrocytic glutamate [25]. Furthermore, a dramatic increase in astrocytic ATP synthesis and release is associated with increased production of connexins, the constituent polypeptides that join to form gap junctions [8]. Additionally, inhibition of astrocyte gap junctional communication by ATP depletion is reversed by calcium sequestration [47].

* *E-mail address:* jimrobertsonmd@yahoo.com (J.M. Robertson).

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PII: S0928-4257(02)00013-X

2.2. Explanation

Neurons rapidly transmit information over long distance. However, there is no compelling evidence that they function to integrate information.

The discovery of action potentials and their rapid transmission along axons led physiologist to conclude that the "messages" conveyed from peripheral sensory receptors and cortical association areas are encoded in the frequency of these potentials. This led von Neumann [49] to conclude that information processing within the brain was "prima facie digital" based on the binary character of these potentials.

The "significance of the precise timing of the axonal spikes is at the moment a matter of much debate" [10]. This current lack of understanding synaptic activity and its relation to global brain functions following a century of research has resulted in a reevaluation of the composition of synapses [42].

An important impetus for this reassessment has been research by gliobiologist. They have demonstrated that virtually all neurotransmitters and neuropeptide receptors are concentrated in astrocytic processes that are in close proximity to all synapses and, like neurons, are capable of responding to these signals in complex ways [5,13,20,38].

All neurotransmitters known to be associated with consciousness (e.g. glutamate, norepinephrine, acetylcholine, serotonin and dopamine) have been identified on astrocytes. These are linked to the agonist-specific generation of calcium signals that are "an early stage of integrating and processing incoming information" [48].

Furthermore, the joining of individual astrocytes into networks of functional syncytia allows the formation of complex levels of communication compartments that are necessary for an intricate process such as consciousness.

A bi-directional flow of information between neurons and astrocytes has been established [5,20]. This has led to the concept of the "tripartite synapse". The addition of astrocytic filopodial terminal processes to axonal and dendritic processes that constitute the classical synapse has been proposed [1].

The Astrocentric Hypothesis proposes that the synapse is the penultimate step in information processing. The final stage leading to consciousness, memory formation and other higher cortical functions occur within cortical astrocytic syncytia after information is originally transferred to the receptors of astrocytic processes at each tripartite synapse.

3. Display of consciousness

Binding of sensory information is necessary but not sufficient for consciousness. Integrated information must be physically displayed within the brain for consciousness to occur. Astrocytic gap junctions, in addition to syncytia formation, have the potential to display such information within these networks. Additionally, these must be intimately associated with parallel neuronal networks in order to respond to intentional conscious decisions.

3.1. Explanation

Research specifically utilizing astrocytic gap junctions strongly support the proposal that these structures are important in representation of consciousness as follows:

1. Gap junction communication in astrocytes is directly related to neuronal firing, synaptic activity and neurotransmitter receptor stimulation [16,30,39,41].
2. Many chemicals that alter consciousness, or induce loss of consciousness, directly affect astrocytic gap junctions. This includes the halogenated anesthetics halothane, enflurane and isoflurane and the intravenous anesthetics propofol and etomidate [33]. Anandamide, an active compound in marijuana [46], and oleamide, a naturally occurring sleep-inducing lipid, also affect gap junction conduction in astrocytes [17].

Furthermore, the following general structural and physiochemical properties of gap junctions qualify these structures for serious consideration as the site of conscious display.

1. Gap junctional plaques "provide a high mechanical stability to the gap junction as a whole as well as to individual channels in the aggregate" [50]. A molecularly rigid structure of this type has been proposed as a platform for intracerebral display of consciousness.
2. Plaque formation can result in diverse structural and functional expressions [3,27,43]. This is critical for a process that integrates diverse sensory data and is intimately associated with attentional and memory systems.
3. Gap junctions and gap junctional plaques rapidly assemble from pre-existing precursors [4,37,44].
4. "Gap junctions are formed by proteins with unusually rapid turnover times" [2,14,29,31,45].
5. Most second messengers including Ca^{2+}, K^+ Na^+, H^+, IP3, cAMP, cGMP, ADP, ATP, as well as amino acids, vitamins and sugars, can either pass through gap junction channels or directly affect gap junctional and perijunctional proteins [28,32,45].
6. Gap junctions synchronize tissue behavior and phase-lock calcium oscillations [6,7,23,40]. Synchronous activity is thought to underlie the temporally dynamic conscious state.

4. Memory formation

Gap junctional plaques readily convert to a long-lived, "closed, high-resistance state" [21,35] by conversion to a crystalline configuration. This feature provides a mechanism for memory formation.

4.1. Explanation

Memory is retention of perceptions. Therefore, a process that converts astrocytic plaques that are activated during consciousness into an inert form to be reactivated later would, by definition, be memory.

Calcium wave activation of calmodulin likely initiates plaque crystallization [35]. Memories would form simultaneously on the same astrocytic gap junctions that consciousness is displayed if this process is verified.

Massa and Mugnaini [34] have confirmed that many "interastrocytic gap junctions are packed in a crystalline array." Iconic, short-term, intermediate and long-term memory could all be formed by this process. The specific type would depend on the interval of time elapsed before the process is reversed.

5. Discussion

Previous attempts to understand consciousness have been unsuccessful. Crick [9] has stated, "I believe that the correct way to conceptualize consciousness has not yet been discovered and that we are merely groping our way toward it. This is one reason why experimental evidence is important. New results may suggest both new ideas and also alert us to errors in old conceptions." The Astrocentric Hypothesis is based on experimental evidence gained over the past 15 years. Ironically, such evidence comes from research on glia and not neurons.

The hypothesis is novel and unorthodox. The unconventional nature of the proposal stems from the fact that all previous attempts to explain consciousness are based on the premise that there is no anatomical region that integrates parcelated sensory information in a unified manner. This has been the prevailing dogma for over a century since William James [24] first pointed out that "there is no cell or group of cells in the brain of such anatomical or functional pre-eminence as to appear to be the keystone or center of gravity of the whole system."

This point of view was recently re-emphasized by Semir Zeki [51] and supported by his research on visual perception. He based the Theory of Multistage Integration on his conclusion that "the anatomical evidence shows no single master area to which all the antecedent areas exclusively connect. Instead the specialized areas connect with one another, either directly or through other areas." Zeki therefore proposed a "network of reentrant connections" as the basis for integration of diverse visual perceptions.

Subsequent attempts to explain consciousness are based on Zeki's theory. Current models incorporate his concept of reentrant connections to account for integration of all sensory modalities. These generally speculate that "reverberating" or "recurrent circuits" are present in thalamocortical projections [9,15] or "convergence regions" [11] and that, consequently, consciousness is expressed in an "emergent" manner "after a certain degree of neurological complexity is reached" [36]. It is probable that these efforts are not satisfactory because the basic assertion that there is no anatomical entity that integrates sensory information is erroneous.

Zeki himself states, "the simplest way (for specialized areas to interact to provide a unified image) would be for all the specialized areas to communicate the results of their operations to one master area, which would then synthesize the incoming information" [51]. The Astrocentric Hypothesis assumes that the brain does incorporated information in the "simplest way." A syncytium of protoplasmic astrocytes comprises the anatomic locus of sensory integration.

Gliobiologist over the past 15 years have increasingly narrowed the distinction between astrocytes and nerve cells, especially postsynaptic neurons. Both cell types are similar morphologically in that they are collectively pleomorphic. They also have similar receptors and release neurotransmitters following stimulation [5,20]. Both are regionally and functionally organized.

"Astrocytes of the cortical gray matter have elaborate dendritic morphologies, superficially similar to those of neurons, and their fine processes mingle intimately with those of neurons throughout the synaptic neuropil. These structural features hint at signaling or even information-processing functions" [12].

The accumulated data strongly supports the role of the protoplasmic astrocyte as a specialized anaxonic post-synaptic cell. This is the cell-type predicted to comprise the final common pathway of information processing and expression of consciousness.

Syncytia formation is the most obvious difference between astrocytes and neurons. It is the formation of syncytia that permits binding of all systems by the conduction, integration and synchronization of calcium waves that encode information initially transmitted to astrocytes from individual synaptic terminals.

The majority of neuroscientists at the beginning of the twentieth century believed that the nervous system was a "syncytium of cells connected to each other by protoplasmic bridges—a concept that solved the problem of continuity since, in it, the flow of information was unimpeded. Then Raymon y Cajal's neuron doctrine interrupted this bridge at the membrane boundary of every cell. Swept out with the syncytium were all the physiological notions of energy and information associated with it" [22].

The Astrocentric Hypothesis postulates that the original assumption was correct: gap junctions provide the "protoplasmic bridges" that connect the "syncytium of cells". However, the cells within the syncytium are astrocytes and not neurons.

Acknowledgements

I wish to express my gratitude to Dr. Francis Crick, Dr. Rolf Dermietzel, Dr. Christian Giaume and Dr. Pete Laming for their constructive criticism and invaluable suggestions regarding the publication of the manuscript. Thanks are also extended to Dr. Giorgio Carmignoto and Dr. Philip Haydon for their expressed interest in the project.

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