REVIEW ARTICLE

Consciousness and Cell Memory: A Dynamic Epigenetic Interrelationship

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ABSTRACT: There have been great advances in the neurological sciences in recent years including some in the higher functions of the brain such as memory but one of the more critical of these with close ties to memory is consciousness which remains an enigma. Revolutionary developments in genetics during the last two decades, referred to as epigenetics, have provided opportunity for discovery. The chromatin in the cell nucleus consists mainly of DNA nucleotides and histone proteins and the DNA is dynamically and epigenetically altered by the local actions of enzymes and trans-acting factors on the adjacent histone amino acids. DNA is also directly activated or inhibited by methyl groups and by non-coding RNAs. Epigenetics is a determinant in long-term cell memory consolidation and, as recently demonstrated in animal and human studies and described here, these effects enable a rapid and extraordinarily complex cognitive matching of cell memory to experience during consciousness.

RÉSUMÉ: Conscience et mémoire cellulaire : une interrelation épigénétique dynamique. Au cours des dernières années, de grands progrès ont été réalisés en neurosciences, entre autres dans le domaine des fonctions cérébrales supérieures telles la mémoire. Cependant, une de ces fonctions très importantes, qui a des liens étroits avec la mémoire, est la conscience et elle demeure une énigme. Des découvertes majeures dans le domaine de la génétique au cours des vingt dernières années, soit l'épigénétique, ont ouvert la voie vers de nouvelles découvertes. La chromatine du noyau cellulaire contient principalement de l'ADN constitué de nucléotides et d'histones et l'ADN est modifié de façon dynamique et épigénétique par les effets locaux d'enzymes et de facteurs trans-régulateurs agissant sur les acides aminés des histones adjacentes. L'ADN est également activé directement ou inhibé par des groupements méthyle et par des ARN non codants. L'épigénétique est un déterminant de la consolidation de la mémoire cellulaire à long terme et, tel que démontré récemment par des études chez l'animal et chez l'humain et tel que décrit dans cet article, ses effets permettent un couplage cognitif rapide et extraordinairement complexe de la mémoire cellulaire à l'expérience pendant l'état de conscience.

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Consciousness may be the most complex and essential cognitive state of the brain. Difficult to define it is generally simply described as the awareness of one's self, thoughts and surroundings. In the clinical neurosciences the level of consciousness in patients with traumatic brain injury (TBI) is the still widely used long-standing state of the art Glasgow Coma Scale designed by Teasdale and Jennett.[1] Grades are given in three categories: eyes open and responses to stimuli, verbal utterances and motor responses to stimuli. Clinically, severe brain injuries are divided into coma, vegetative state (VS) and the minimally conscious state (MCS). In coma the sleep-wakefulness cycle is absent, eyes are closed and the patient is unarousable and unresponsive to stimulation.[2,3] In VS and MCS patients the sleep-wakefulness cycle is intact and their behavior is mainly the result of severely damaged cerebral hemispheres with a relatively intact brainstem.[4] The VS patients typically open their eyes, respond to noxious stimuli and may display spontaneous movement but show no evidence of an awareness of self or the environment.[5] However, Owen and associates[6,7] using functional magnetic resonance imaging (fMRI) have demonstrated islands of cerebral cortical activity in the parahippocampal, posterior parietal and the lateral premotor cortices in VS patients and normal control subjects in response to verbal commands such as "imagine playing tennis". The authors interpreted this as a sign of the patient being "consciously aware" in their apparent willingness to follow instructions although others are more skeptical or consider the level of consciousness as more consistent with MCS than VS.[3] Nonetheless, the activity on the scan showed intact neural pathways compatible with a verbal auditory memory trace, possibly in a dream-like state without the patient being aware of the actual circumstance or surroundings. The MCS patients, although they were sometimes severely impaired, showed some

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awareness of self and the environment and could fix their eyes on objects, follow simple commands and produce some intelligible speech either vocally or by gesture and thereby indicate, through their actions, consciousness.[3,6,8] The fMRI in these patients showed reproducible cortical activity to spoken language and tactile stimulation confirming the potential in some MCS subjects for mnemonically processing cognitive and sensory functions.[9]

There is obvious risk in claims for or against consciousness in VS and MCS patients because interpretations are judged on behavior rather than neurophysiology. Moreover, the extent of brain injury and its effects vary enormously. From a common perspective consciousness is perceived as dualistically separated into mind and matter even among the most scientifically well educated persons indicating how little is known biologically of the higher brain functions as they relate to our existence and survival.[10,11] Yet knowledge, especially in how the mind works, is the only venue for change in beliefs. Current understanding of consciousness as related to wakefulness and dependent on rapid memory access is well described in the literature and only briefly presented here.[12,13] This is followed by a discussion of recent developments in epigenetics especially in relation to memory, DNA methylation, non-protein coding RNAs and synaptic tagging in neurons as they offer novel insight into how information can be stored and accessed through cell memory and applied to consciousness.

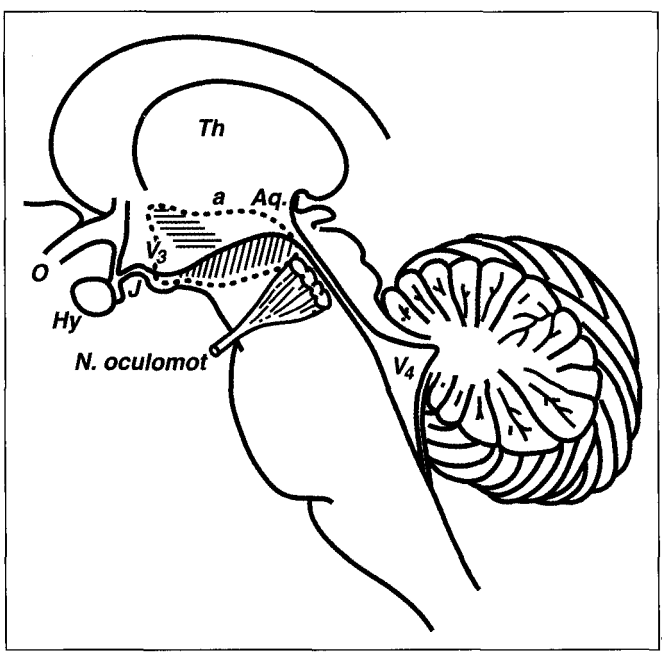

Figure 1: *An original Illustration by von Economo[16] showing the lesions in the hypothalamus and midbrain as they occurred in encephalitis lethargica. The diagonal cross-hatching in the midbrain, rostral to the oculomotor nucleus, represents inflammation that he interpreted as the cause of the sleepiness and ocular palsy. The horizontally cross-hatched region in the anterior hypothalamus he ascribed to a "tormenting" insomnia in an earlier period of the illness (with permission, Wolters Kluwer).*

The Arousal System and Memory Consolidation

The sleep-wakefulness cycle is generated by the reticular activating or 'arousal' system in the midbrain and its absence in coma following TBI is generally a sign of a lesion in this region.[14,15] Wakefulness is associated with consciousness as deep non-rapid eye movement (REM) sleep is to unconsciousness from which the sleeper can be fully aroused. Von Economo[16], almost a century ago, discovered lesions in the upper midbrain and posterior hypothalamus in cases of encephalitis lethargica and a few decades later Magoun and associates demonstrated how lesions in feline midbrain tegmentum produced unarousable sleep, vis à vis coma (Figure 1).[14,17,18] The cortical, subcortical and spinal cord connections of the arousal system have since been expanded to include complex networks of nuclei in the brain stem and hypothalamus.[19] Two pathways from the arousal system project to the cerebral cortex: (i) a dorsal thalamic path activates multiple nuclei in the thalamus, notably those receiving sensory input, and project to the thalamic reticular nucleus which relays information via the internal capsule to the cerebral cortex, and (ii) a ventral hypothalamic pathway, joined by axons from nuclei in the lateral hypothalamus, extends to the basal forebrain and from there extensively targets and activates neurons in the cerebral cortex.[13,20]

The influence of the arousal system on wakefulness and sleep is regulated by the suprachiasmatic nucleus, the master circadian pacemaker of the brain in the anterior hypothalamus, with the participation of other hypothalamic nuclei.[19] By facilitating sensory input to the cerebral cortex during wakefulness the arousal system stimulates the matching of incoming information to existing memories in the cerebral cortex.[20,21] Thus, consciousness of the environment is dependent on the arousal system and the distribution of sensory input to appropriate regions of the brain. As suggested by Evans[21] it is "the power source of the cerebral hemispheres" but memory is a critical component of consciousness in how it is accessed with the precision and speed required for a continuous flow of environmental sensory input that must be very rapidly matched to memory in multiple areas of the cortex.[22]

The brain is a storehouse of memories and long-term memories accumulate over much of a normal lifetime of sensory inputs together with cognitively and emotionally derived schemata. The hippocampal formation (hippocampus, dentate gyrus and subiculum) and the adjacent entorhinal cortex, parahippocampal gyrus and perirhinal temporal lobe cortex record new memories. However, the hippocampus is also involved in the retrieval of recent memories and it is generally believed that longer duration memories become consolidated in the neocortex and are ultimately retrieved independently of the hippocampus.[23] But some recent studies illustrate how the storage and recall of memory is a more subtle process. As postulated by Takashima et al, the hippocampus rapidly encodes new information whereas the neocortex adapts relatively slowly to its transfer and assimilation into preexisting memory.[24] As described by these authors the anatomical connectivity of the hippocampus extends over a wide range of areas in the brain and a solitary sensory stimulus, such as the image of a face, may stimulate a network of several functionally distinct representational neocortical regions (see also Levine et al and

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Friston et al).[25,26] With consolidation of memory, functional connectivity between the stimulated neocortical areas increases and the hippocampal activity and its connections gradually decrease. However, recently incorporated information in the representational neocortical areas remains independently accessible by the parahippocampal and perirhinal cortices in what is termed 'recognition memory' as when, for example, a face is recognized as familiar during the exploration of an otherwise novel situation.[27-29] The capacity of the brain to hold information in memory during multiple tasks and accurately and swiftly associate names with objects or solve problems from assembled bits of information represents functions whereby access to widespread cortically stored information is being matched. In the context of being conscious and visually scanning and recognizing our surroundings there is a constant and extraordinarily rapidly changing response to sensory input taking place in neurons in cell memory wherein epigenetics has a critical role.

Epigenetics and Cell Memory

Whereas DNA has been considered a stable and biologically unalterable genetic blueprint for protein coding by RNA, both concepts are fading with the recent and rapidly developing discoveries of nuclear chromatin remodeling, epigenetics and non-protein-coding RNAs. In 1998, Fire et al[30] demonstrated how non-coding double-stranded RNA converts to short single strands and silences messenger RNA (mRNA).[30] RNAs derived from non-protein-coding segments of DNA, such as introns and parts of exons, have also recently been described and their function appears mainly as one of a number of mechanisms involved in the epigenetic regulation of DNA transcription.[31] Epigenetics is defined as the study of changes in gene expression that occur without a change in DNA sequence but is produced instead by modifications in the chromatin proteins in the cell nucleus.[32,33] It is a means whereby the germline cells of an organism with their identical DNA sequences can be terminally differentiated into a variety of cell types.

Chromatin and Gene Regulation

The cell nucleus consists of chromatin that is a complex of DNA, RNA, histone and a large assembly of nonhistone proteins including modifying enzymes and trans-acting factors. A nucleosome is a bead-like chromosomal structure within the chromatin consisting of eight histone proteins (octamer) wrapped by a segment of DNA of about 147 base pairs in length.[34] The octamer is formed by two copies each of four histones labeled H2A, H2B, H3 and H4 (Figure 2). Short amino acid linkers and accompanying DNA of about 50 base pairs, join the octamers giving them an appearance of beads on a string.[35,36] The nucleosome exists in two forms: a genetically inactive tightly compacted heterochromatin and a genetically active DNA-transcription factor accessible euchromatin. Extending from the core of the nucleosome of all eight histones are short (about 40 amino acids) tails where euchromatin activity takes place. The contiguous arrangement of the DNA and histones in the tails is such as to enable full access of RNA polymerase II, transcription factors and the many modifying enzymes to both elements permitting genetic and epigenetic expression (Figure 3). The amino acids in the tails are subject to "post-translational"

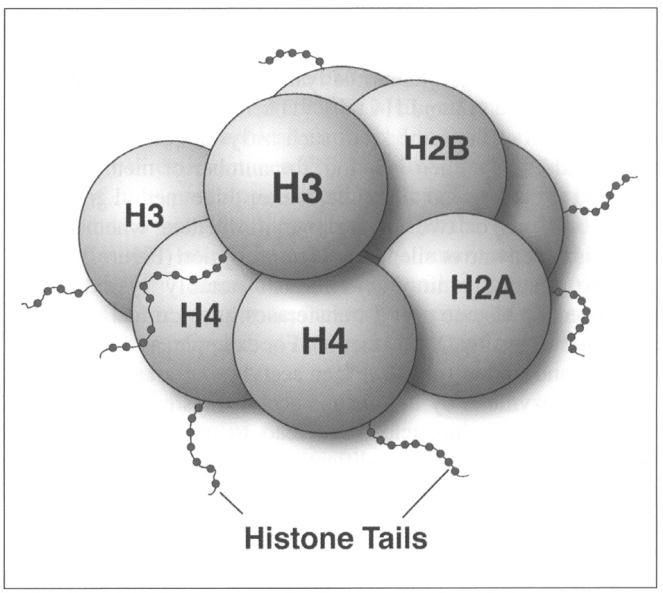

Figure 2: *A nucleosome histone octamer with tails. The octamer is formed by two copies of H3, H4, H2A and H2B core histone proteins and each has an N-terminal and C-terminal tail although the N-terminal is considered by Keppler and Archer to be the most active.*[39]

(structural) modification by the covalent attachment of methyl, acetyl and phosphoryl groups and thereby producing electrostatic charge effects on the adjacent DNA. The attachment or removal of the methyl, acetyl and other groups to the histone tail is achieved by trans-acting factors and enzymes such as, respectively, histone methyl or histone acetyl transferases and corresponding histone demethylases and deacetylases.[33,37-40]

The interaction of the histone proteins with DNA is extraordinarily complex but can be summarized as follows.

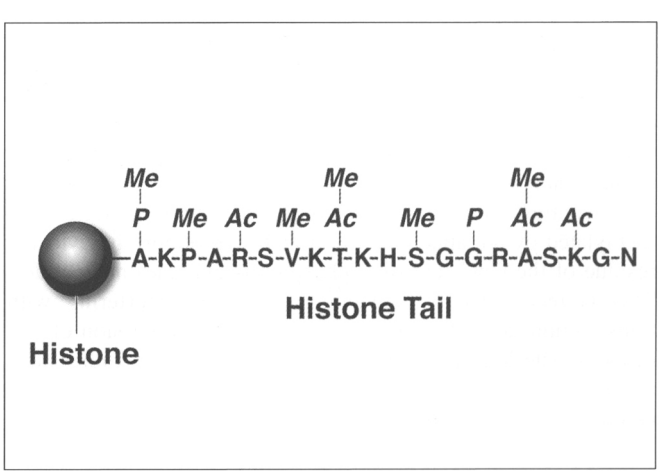

Figure 3: *A histone protein tail consists of amino acids as represented by the single letters e.g. lysine (K) and alanine (A). The superimposed letters attached to some of the amino acids represent methyl (Me), acetyl (Ac) and phosphoryl (P) groups and these modify the epigenetic effect of the amino acid on an adjacent region of the DNA (not shown).*

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Histone methylation has mainly regulatory RNA transcriptionaly positive and negative effects and these have been linked to the location of the large number of lysine and arginine residues in the euchromatin H3 and H4 tails.[41] There can be several amino acid residues of the same kind, such as lysine, on a histone tail and, in addition to their location, the number of methyl groups attached to each amino acid (one, two or three methyl groups on lysine and one or two on arginine) influences whether their action is to activate or silence gene transcription (Figure 3).[36,42,43] Nuclear histone amino acids, most notably lysine, when acetylated by histone acetyl transferases have critical and quite extensive effects on DNA function. For example, as described by Keppler and Archer (p. 1302)[39], an acetyl group transferred from acetyl-coenzyme A by the histone acetyl transferases to certain histone lysine amino acids, can lead to an 'open chromatin conformation' and other modifications culminating in increased transcriptional activity.[39] This is attributed to the acetyl group neutralizing the positive charge on lysine. Accordingly, deacetylation of the lysine by histone deacetylases, in revealing the positive charge, allows for "histone tail-DNA interaction and heterochromatin compaction" and thereby the inactivation of the DNA.

Phosphorylation also has an extensive regulatory influence on histones, especially on transcription, that can be either activation or inhibition with phosphoryl groups attached to either serine or threonine residues in the tail.[40] It has also been associated with mitosis, DNA repair, chromosome condensation and apoptosis. It can act synergistically with histone acetylation. Its effect is considered by Keppler and Archer[40] to be due to the addition of "a single negative charge to the histone, thereby altering chromatin structure and influencing transcription by facilitating interactions with transcription factors and other chromatin machinery".[40] Two additional modifiers of histones are ubiquitin and a small ubiquitin-related modifier (SUMO) and these may act synergistically with histone acetylation.

The epigenetic histone and DNA modifications in the nucleosome which control gene expression respond to the metabolic state and the immediate extracellular environment of the cell.[44] In the brain the extracellular environment of the neurons is predominantly synaptic input from other neurons and in the hippocampus, this includes sensory information derived from humoral and/or extracorporeal somatosensory, visual, auditory, etc. receptors. Epigenetic changes induced by the conditions within or outside a cell can be preserved by long-term plasticity and may be propagated by somatic and germline cells as inheritable traits.[45,46]

In contrast to epigenetic histone methylation, DNA can be methylated by the attachment of a methyl group to the cytosine residue of the CpG (cytosine phosphorus guanine) nucleotides. This is recognized as silencing a gene by interfering with transcription factor binding as occurs in the suppression of one of the female X chromosomes.[47,48] However, recent studies have shown how both methylation and demethylation of DNA are essential to memory formation in the brain.

DNA Methylation in Memory Consolidation

Kandel and coauthors in studies of repetitive noxious sensory stimuli applied to the sea snail *Aplysia californica* demonstrated how memory storage of the experience in the nervous system begins with molecular mechanisms at the cell level wherein short and long-term memory of sensory input correlates with the frequency and strength of synaptic stimulation and the synthesis of protein (plasticity).[49-51] The protein synthesis was identified with the activation of the transcription factor cAMP-response element binding protein-1 (CREB-1) in the promoter region of target genes in the cell nucleus by protein kinase A (PKA) and mitogen-activated protein kinase (MAPK). Evidence has since accumulated on how these cellular processes are the outcome of nuclear transformations and a lifelong storage of molecular information in cell memory as required for the normal development and mitotic perpetuation of phenotype.[48] This is possible because epigenetic histone modifications alter how DNA is accessed and provide genetic responses that are appropriate to the function and environmental conditions of the cell. But it has not been clear how epigenetic processes are regulated. A response to this was provided by Sweatt and associates in studies on the effect of fear conditioning on memory in rodents by sensory stimulation in the form of electrical foot shock during their exploration of a training chamber.[48] They found that DNA methylation by a DNA methyltransferase in the neurons of the adult hippocampus is a key regulatory element in the consolidation of long-term cell memory.[48,52,53] Whereas the attachment of methyl groups to the CpG dinucleotides in DNA had hitherto been linked exclusively to gene silencing and considered physiologically unalterable in neurons, a number of investigators have recently found active DNA methylation and demethylation of the CpG dinucleotides in mature cells as may serve new memory formation.[48,52,54-57] DNA methylation controls the transcription of a number of genes in the nervous system such as the brain-derived neurotrophic factor *(bdnf)* and the modulator of synaptic function *reelin (Reln)*.[53,57] The importance of these observations lies within a determination of how epigenetic functions of DNA contribute to cell memory on information received from enormous numbers of synapses (estimated average of 38,000) per neuron in the human cortex.[58] How this may be accomplished is described in recent accounts of 'synaptic tagging'.

Synaptic Tagging and Cell Memory

How memory is encoded in the genome of neurons and provides the basis of cognitive states as generated by vast numbers of synapses on their dendrites and somata seems incomprehensible. However, Frey and Morris[59] may provide a solution in their 'synaptic tag' hypothesis wherein the transmission of electrical impulses by an axon to a dendritic spine triggers a signal, referred to as a synaptic tag, that stimulates the production of plasticity-related proteins and long-term potentiation (LTP) in the spine as, electrophysiologically, this is related to long-term memory.[60] The synaptic tag is defined by the authors as "a hypothetical mark present in synapses expressing early-phase plasticity" and although the tag has not been positively identified there have been a number of suggestions such as a protein kinase or, more likely, a local distinguishing mark of the synapse related to its particular axonal input.[61,62] Long-term potentiation is dependent on protein synthesis and requires repeated synaptic inputs to attain long-lasting synaptic strength (late-phase plasticity) as required for long-term memory. Although LTP is dependent on protein

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synthesis in the synapse, essential genetic materials such as mRNA and ribonucleoproteins must be packaged and transported on microtubules from the cell nucleus to a dendritic spine by kinesin motor proteins as proposed by Bramham and Wells (Figure 4).[63] Epigenetics has a major role in the design and provision of genetic products delivered to a synapse. Each dendritic spine, from the standpoint of genetic tagging, must be synaptically adapted and responsive to information that is delivered to it from another neuron. As this involves many thousands of synapses, an individual neuron must play many parts since these represent its participation in large numbers of neural networks.

A familiar form of synaptic tagging and neural networking, first described by O'Keefe and Dostrovsky, is the "spatial reference map" in the hippocampus of freely moving rats that formed during their explorations of a training platform.[64] Spatial networking as it computes the location, direction and distance travelled by a animal in a spatial environment is encoded by pyramidal neurons referred to as place cells in the hippocampus and grid cells in the entorhinal cortex. The synaptic firing patterns of the individual hippocampal place cells represent the positions taken by the animal and, when the firing fields of the cells overlap, their synaptic activity increases and produces long-term synaptic plasticity.[65-67] In this manner the strength of synaptic connections between place cells form a cognitive map of the directions and distances taken by the animal. The place cells relay information to the entorhinal grid cells and although the mechanism of their interaction is, as yet, unresolved the grid cells are also topographically arranged in the form a map of the space and directions taken.[68,69] The entorhinal cortex contains most of the parahippocampal cortex and is reciprocally connected to both the hippocampus and the perirhinal cortex and, via the latter, is extensively interconnected to the neocortex.[12,70,71] Individual place and grid cells conjointly form networks of the many routes taken in a spatial environment and this may be accomplished by different synaptic connections on the same neurons.

Prefrontal Control of Memory

The prefrontal cortex has 'executive functions' in the processing of memory that are mainly the following. The frontopolar cortex, as proposed by Koechlin and Hyafil, "forms the apex of the executive system underlying decision-making" but is limited to "protecting the execution of long-term mental plans from immediate environmental demands".[72] As the authors note the frontopolar cortex may have a role in rewarding complex behavioral and cognitive routines rather than in

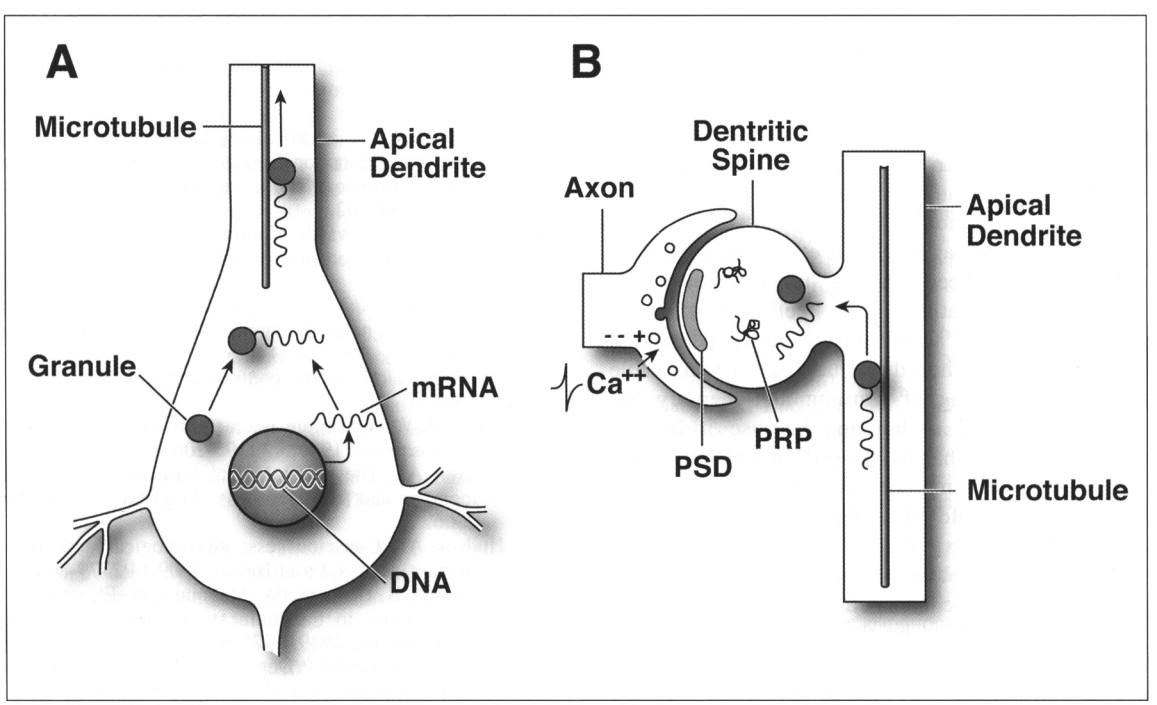

Figure 4: *Synaptic tagging. A hypothetical model for the translation of mRNA to protein in a dendritic spine of a neuron. (A) Cell body. The mRNAs are formed in the nucleus where their translation property is inhibited and on release to the cytoplasm they are attached to RNA granules and delivered on a microtubule to a newly forming synaptic spine on a dendrite.[59,61,63] (B) Apical dendrite. Granules bearing the mRNA on arrival at a synaptic spine release the mRNA. The translation properties of the mRNA are restored and, with the participation of support proteins and enzymes in the postsynaptic density (PSD), the synthesis of plasticity-related proteins (PRPs) begins. On completion the synapse is presumed to form an unique paired relationship between the two neurons.*

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physically challenging environmental situations involving survival, which require complex decision-making and reasoning. In the performance of a previously learned task an area for working memory in the dorsolateral prefrontal cortex becomes engaged in the selection of memories that are required in the undertaking of a task, as well as subsequent requirements for its completion.[73,74] Working memory enhances by way of top-down control visuospatial memory storage capacity in the posterior parietal cortex, although, in studies by Edin et al[75], individuals differed in the strength of its application. Injury to the medial and ventral (orbitofrontal) areas of the prefrontal cortex is described by Damasio as producing "a pattern of abnormal decision-making which is most notable in personal and social matters".[76] Both medial and orbitofrontal cortices have extensive cortical and subcortical connections, notably with the striatum, hippocampus, cingulate cortex, amygdala, hypothalamus and the autonomic brain stem nuclei which have an especially visceral influence on consciousness.[12,77] The human brain has a large prefrontal cortex compared with subprimate mammals and proportionately larger than in subhuman primates and has evolved, we can assume, to accommodate our more advanced cognitive abilities.[78,79]

Conclusion

Consciousness as a normal state of life receives little consideration until it is lost whereupon attention is given to the cause and treatment. Protracted loss of consciousness, as in coma and the vegetative state, involves lengthy care and treatment and when it appears irreversible there are ethical issues such as the withdrawal of treatment.[80,81] In the vegetative state there is always uncertainty of whether the patient is actually unconscious but recent fMRI findings have provided evidence of awareness in several cases.[6] The finding of an appropriate cognitive memory trace in response to an environmental challenge in presumably unconscious patients has raised the humanitarian stakes on a need for understanding the physiological mechanisms underlying consciousness.

Three and a half decades ago Schmitt et al expressed their concern with how there has been a lack of "unifying conceptual principles capable of relating brain cell activities to psychological processes such as learning, memory, perception and consciousness".[82] Since then there has been a remarkable advance in our understanding of learning and memory but consciousness has remained a dilemma because it has no defining characteristics other than as 'the self' of which there are many wide-ranging views even among cognitive scientists with little in the way of a finite physiological interpretation.[83] However, as argued by LeDoux,[83] the self is probably encoded in cell memory "To the extent that the self is a set of memories, the particular patterns of synaptic connections in an individual's brain and the information coded by these connections are the keys to who that person is" (p. 298, LeDoux[84]). In context with this, consciousness would also be coded in memory. In the present review, recent developments in epigenetics are presented as they provide support for this concept.

The most significant characteristics of epigenetics are how non-coding RNAs and the post-translation effects of the histone proteins on DNA regulate the genome. Direct inhibitory and facilitatory effects on DNA by methylation have also become a major influence. Moreover, synaptic tagging permits a neuron to respond to individual synaptic contacts and thereby a single neuron may participate in multiple networks. The concept of consciousness being identical to self and based on memory is difficult to accept because, as we see ourselves as humans, we are willful and make independent decisions on how we behave and sustain our lives. Indeed, the prefrontal cortex has what is generally considered a dominant role in decision-making.[75] Nonetheless, from birth we have visceral, somatosensory and other sensory stimuli phenotypically personalized in memory at the cell level accounting for much of our sense of self and providing a unifying conceptual principle of consciousness.

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