Consciousness and general anaesthesia: Recent View

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Abstract

An explanation of consciousness is one of the major unsolved problems of modern science. The modern view of consciousness arose in the nineteenth century; the view presumed that mental activity correlates with distinct physical states. Is the problem of consciousness real? Crick and Koch made a tentative assumption that all different aspects of consciousness (pain, seeing, thinking, emotion, self-consciousness) are connected by a basic common mechanism. The next step towards understanding involved the neuronal theories of consciousness (correlates of consciousness), often referred as the NNC (neural correlates of consciousness). Many neuroscientists presume that consciousness must have a neuronal correlate.
The neuroscience of anaesthesia can be defined as studying the effect of anaesthetic agents on consciousness and the preconsciousness brain mechanisms of cognitive function. Some of these mechanisms, such as recognition of the novel stimuli, are still present in deep anaesthesia, during continuous suppression. Anaesthesia is not "an all or nothing" phenomenon and consciousness awareness with explicit memory represents only one part of the spectrum of cognitive functions. The introduction of safe general anaesthesia represents one of the most important, although under-appreciated, advances in modern surgery. There is some difficulty in defining the term "consciousness" in relation to the anaesthetic state. The difference in brain activity between those under anaesthesia and those not under any such influence.

R E V I E W

INTRODUCTION

History and theory of consciousness

Mind and brain are different entities (mental versus physical entities) that exist independently while at the same time interacting and running parallel. When you look at how far we've still got to go to explain the hugely complicated organ which we call our brain, with all the processes which are not only transient but also capable of interacting in the most intricate ways, if becomes clear that we are only at the very beginning of the journey. The abstract noun "consciousness" is not frequently used by itself in contemporary literature; it was originally derived from the Latin "con" (with) and "scire" (to know) (Crick, 1994). Consciousness is a quality of the mind generally regarded to comprise qualities such as subjectivity, self-awareness, sentience, sapience, and the ability to perceive the relationship between oneself and one's environment. It is a

subject of considerable research in the fields of philosophy of the mind, psychology, neuroscience, and cognitive science.

The mind-body dualism is a formal construct of modern philosophy. Functional frameworks for consciousness stem metaphorically from the 17th century French philosopher Rene Descartes' "Theatre of Consciousness" (Baars, 1997). His famous "cogito ergo sum" ("I think therefore I am") implies that only through personal consciousness can one be certain of one's own existence. He identified consciousness with mind or soul, which to him was a substance, as real and as concrete as the substance of the body. Descartes defined body as extended (space-filling), physical and material; he defined mind as "thinking thing" (res cogitans), which was unextended (did not take up space) and was not made of any physical material, and was purely spiritual. He also posited that these two substances mutually affect each other, and termed this affect "interactionism." It is worth noting that this term is unrelated to the interactionism associated with the German theorist Max Weber. During the 1800's, neurologists, and of course the great American psychologist William James, wrote about attention as being fundamental to the idea of human consciousness. A definition very similar to that of James (1892) is currently offered for the psychological dimension of consciousness: at a minimum, normal consciousness consists of aserially time-ordered, organized, restricted and reflective awareness of self and the environment. Moreover, it is an experience of graded complexity and quality. Perhaps the most commonly used contemporary notion of the conscious mental state was captured by Thomas Nagel's famous "what it is like" sense (1974).

In approaching the problem, the tentative assumption was made (Crick and Koch, 1990) that all the different aspects of consciousness (for example, pain, visual awareness, self-consciousness**,** etc.) employ a basic common mechanism or perhaps a few common mechanisms. The personal decision (Crick and Koch, 1990) that several topics should be set aside or merely stated without further discussion, for experience had shown that otherwise valuable time can be wasted arguing about them without coming to any conclusion.

There are many forms of consciousness, such as those associated with seeing, thinking, emotion, and pain. Self-consciousness means the self-referential aspect of consciousness and is probably a special case of consciousness. Francis Crick (1994) has suggested that one way of discovering the neural basis of consciousness is to identify:

1. those neurons that are active during conscious states and inactive during states when consciousness is absent, and
2. those neurons whose activity is unaffected by the state of consciousness, and then see if it is possible to determine the differences between the two neural populations.

Crick and Koch (1995a) suggested that the biological usefulness of visual consciousness in humans is to produce the best current interpretation of the visual scene in light of past experience, either of ourselves or of our ancestors (embodied in our genes), and to make this interpretation directly available, for a sufficient period of time, to the parts of the brain that contemplate and plan voluntary motor output, including speech. They concluded that the neuron is the basis of consciousness, especially visual consciousness, since vision is the best understood of all the human senses. This astonishing hypothesis is fundamentally that the neuron is the basis of consciousness, just as DNA can be thought of as the basis of life. It's the basis, but remember, the brain does not consist of just a single neuron. The interactions between the billions of neurons in the human brain as well as certain animals, is what produces consciousness; consciousness is a process, not a thing, and the neurons are the actors.

As we increase our knowledge and understanding of the plasticity of neurons, we may find that within a single population of neurons, one type of activity may be associated with conscious states and another with unconscious states. It is theoretically possible that some of the relevant differences that Crick describes between 'consciousness' and 'non-consciousness' neurons may be biochemical. It might be useful to consider what these biochemical factors are.

While most neuroscientists acknowledge that consciousness exists, and that at present it is something of a mystery, most of them do not attempt to study it, **mainly for one of two reasons:**

(a) They consider it to be a philosophical problem, and so best left to philosophers.
(b) They concede that it is a scientific problem, but think it is premature to study it now.

1. NEURONAL CORRELATES OF CONSCIOUSNESS IN HUMAN

Specific brain structures and their functional activities, as they relate to consciousness, are known as the neural correlate of consciousness (NCC). The NCC represent the minimal set of neural structures and events – in this case, synchronized action potentials in neocortical pyramidal neurons – sufficient for a specific conscious percept or conscious (explicit) memory. There is "a specific system in the brain whose activity correlates directly with states of conscious experience" (Crick and

Koch, 1998). There are special sets of "consciousness" neurons distributed throughout cortex (and associated regions and structures, such as the thalamus and basal ganglia) that represent the ultimate NCC, in the sense that activity of an appropriate subset of these is both necessary and sufficient to give rise to an appropriate conscious experience or percept (Crick, 1994). NCC neurons would be characterized by a unique combination of molecular, biophysical, pharmacological, and anatomical traits. All cortical neurons may be capable of participating in the representation of one percept or another. Whenever information is represented in the NCC it is represented in consciousness (Rees *et al*., 2002). The paper about Neural Correlates of Consciousness: *Empirical and Conceptual Questions* was the first published by the MIT Press in 2000 (Metzinger, 2000) and presented at the Association for the Scientific Study of Consciousness conference on "Neural Correlates of Consciousness" in Bremen, June 1998 (Chalmers, 2000). The secret of consciousness may consist of all cortical neurons representing a particular percept at a given moment. The NCC neurons can be demonstrated through clinical evidence, i.e. small lesions of the intralaminar nuclei of the thalamus (ILN), the neurons of which project widely and reciprocally into the cerebral cortex, can cause loss of consciousness and coma. Consequently, ILN neurons have been proposed as the structure representing the seat and possibly the source of consciousness (Bogen, 1995; Purpura and Schiff, 1997). Although, it is more likely that the ILN neurons provide an enabling or arousal signal without which no cortical processing can occur; in which case the intralaminar nuclei of the thalamus represent a neuronal enabling factor for consciousness.

Among neuronal modulating factors are various activities in the nuclei in the brain stem and the midbrain, often collectively referred to as the reticular activating system, which control, in a widespread and quite specific manner, levels of noradrenalin, serotonin, and acetylcholine in the forebrain. Appropriate levels of these neurotransmitters are needed for (i) sleep, arousal, attention, memory, and (ii) other functions critical to behaviour and consciousness. Acute bilateral loss of function of these structures, which are widely and reciprocally connected to the basal ganglia and cerebral cortex, leads to immediate coma or profound disruption in arousal and consciousness. Additionally, small lesions in the brain stem and thalamus of patients can lead to a complete loss of consciousness, while destruction of circumscribed parts of the cerebral cortex of patients can eliminate very specific aspects of consciousness, such as the ability to be aware of motion or the ability to recognize objects or faces, but without a concomitant loss of vision in general.

As was seen earlier in discussing neural theories of consciousness, the search for the so-called "neural correlates of consciousness" (NCC) is a major preoccupation of philosophers and scientists alike (Metzinger, 2000). Determining the precise brain structure, region or function responsible for consciousness is a different and far more difficult enterprise than merely holding a generic belief in some form of materialism. The search for the NCC is arguably the cornerstone in the recent resurgence of interest in the scientific study of consciousness. A number of proposals have been put forward concerning the nature and location of the NCC. Some of these include:

- 40-hertz oscillations in the cerebral cortex (Crick and Koch, 1990)
- Intralaminar nuclei in the thalamus (Bogen, 1995)
- Re-entrant loops in thalamocortical systems Edelman, 1989)
- 40-hertz rhythmic activity in thalamocortical systems (Llinas and al., 1994)
- Extended reticular-thalamic activation system (Newman and Baars, 1993)
- Neural assemblies bound by NMDA (Flohr, 1995)
- Certain neurochemical levels of activation (Hobson, 1997)
- Certain neurons in inferior temporal cortex (Sheinberg and Logothetis, 1997)
- Neurons in extrastriate visual cortex projecting to prefrontal areas (Crick and Koch, 1995a)
- Visual processing within the ventral stream (Milner and Googale, 1995).

The study of consciousness can be divided into several separate questions. Most, if not all of which, can then be subjected to scientific inquiry. The major question that neuroscience must ultimately answer can be bluntly stated as follows: It is probable that at any given moment, certain active neuronal processes taking place within our brain correlate with consciousness, while others do not; if this is the case, what is the difference between them? Whenever information is represented in the NCC it is represented in consciousness. The NCC is the minimal (minimal, since it is known that the entire brain is sufficient to give rise to consciousness) set of neurons (most likely distributed throughout certain cortical and subcortical areas) whose function directly correlates with the perception of a subject at a given moment in time. Conversely, hypothetically stimulating these neurons in the right manner should enable reproduction of the previously realized perception. Discovering the true identity of the NCC and its properties will mark a major milestone in any scientific theory of consciousness.

What is the character of the NCC? The most popular belief has been that consciousness arises as an emergent property of a very large collection of interacting neurons (Libet, 1993) which exceed a certain level of

complexity (Edelman and Tononi, 2000). From this point of view, it would be difficult to imagine that consciousness is located at the level of individual neurons. An alternative hypothesis is that there are special sets of "consciousness neurons" distributed throughout cortex and associated systems. Such neurons represent the ultimate neuronal correlate of consciousness, in the sense that the relevant activity of an appropriate subset of them is both necessary and sufficient to give rise to an appropriate conscious experience or percept (Crick and Koch, 1998). Generating the appropriate activity in these neurons, for instance by suitable electrical stimulation, would give rise to specific percepts. Any one subtype of NCC neurons would, most likely, be characterized by a unique combination of molecular, biophysical, pharmacological, and anatomical traits. It is possible, of course, that all cortical neurons may be capable of participating in the representation of one percept or another, although not necessarily in all percepts. The secret of consciousness would then be the transient activity of a subset of neurons, consisting of all those cortical neurons which represent that particular percept at that particular moment. How the activity of neurons across a multitude of brain areas can encode all of the different aspects associated with, for example a person (e.g., the colour of skin, facial expressions, gender, identity, and voice) can be combined into a single percept remains puzzling and is known as the binding problem.

What, if anything, can we infer about the location of neurons whose activity correlates with consciousness? In the case of visual consciousness, it was surmised that these neurons must have access to visual information, and project to the planning stages of the brain; that is, to the premotor and frontal areas (Fuster, 2001).

Since none of the neurons from the primary visual cortex of the macaque monkey project to any area forward of the central sulcus Crick and Koch (1998) proposed that V1 neurons do not give rise to consciousness (although V1 neurons are necessary for most forms of vision, just as is the retina). Ongoing electrophysiological, psychophysical, and imaging research in monkeys and humans is evaluating this prediction.

While the set of neurons that can express any one particular conscious percept might constitute a relatively small fraction of all neurons in any one area, many more neurons might be necessary to support the percept leading up to the level of the NCC. This might resolve the apparent paradox between clinical lesioning data suggesting that small and discrete lesions in cortex can lead to very specific deficits (such as the inability to see colours or to recognize faces in the absence of other visual losses) and the functional imaging data that indicates that a single visual stimulus can activate large swaths of cortex. Conceptually, several other questions need to be answered about the NCC: (1) What type of activity corresponds to the NCC (it has been proposed, as long ago as the early part of the twentieth century, that spiking activity synchronized across a population of neurons is a necessary condition for consciousness? (2) What causes the neural state associated with consciousness (NCC) to occur? and finally (3) What effect does the NCC have on postsynaptic structures, including motor output? The NCC is the minimal (minimal, since it is known that the entire brain is sufficient to give rise to consciousness) set of neurons, most likely distributed throughout certain cortical and subcortical areas, whose firing directly correlates with the perception of the subject at the time. Neural correlates of consciousness may be identified through a number of methods, including: (i) clinico-pathologic correlation (e.g., in stroke or epilepsy), (ii) functional neuroimaging, and (iii) neurophysiologic recordings in association with a cognitive task.The best scientific evidence for the existence of the NCC comes from brain imaging and electrophysiologic monitoring of loss of consciousness during induction of general anaesthesia.

2. CONSCIOUSNESS

Consciousness is a puzzling state-dependent property of certain types of complex, adaptive systems. The best example of such a system is a healthy and attentive human brain. If the brain is anaesthetized, consciousness ceases. Small lesions in the brain stem and thalamus of patients can lead to a complete loss of consciousness, while destruction of circumscribed parts of the cerebral cortex of patients eliminates only very specific aspects of consciousness, such as the ability to be aware of motion or to recognize objects, without a concomitant loss of vision in general. Given the similarity in brain structure and behaviour, biologists commonly assume that at least some animals, in particular nonhuman primates, share certain aspects of consciousness with humans. Brain scientists, in conjunction with cognitive neuroscientists, are exploiting a number of empirical approaches to shed light on the neural basis of consciousness. Since it is not known to what extent artificial systems, such as computers and robots, can become conscious, this entry will exclude these from consideration.

Since consciousness is one of the principal properties of the human brain, which is a highly evolved system, it therefore can be assumed to have a useful function to perform (Crick and Koch,1992, Crick and Koch,1995b).

Consciousness is a state that defies definition, but which is thought to involve: thoughts, sensations, perceptions, moods, emotions, dreams, and an awareness of self, although not all of the listed elements are necessarily required.

Consciousness involves four functions:

stimulus uptake (perception), stimulus processing (mnemonic representation), stimulus evaluation (emotion), and stimulus response (volition). These processes are integrated through complex neuronal systems to achieve regional linking within one modality, temporal, and semantic binding of information (Pöppel and Schwender, 1993). Contemporary literature (Tsuchiya and Adolphs, 2007) refers to two components that are distinguishable: the level (state) of consciousness (e.g. wakefulness, coma and dreamless sleep), and its content, i.e. that which people are conscious of (e.g. the scent of a perfume or the colour of a rose). Revised scientific summary of emotion and of consciousness provide an unprecedented opportunity for progress in this subject. The common view is that emotion and consciousness emerge as a result of neuronal activity in our brain. Additionally, some explain new emotions or consciousness as relationships between an organism and its environment. Structures that are important with regard to emotion are also important with regard to the level of consciousness. In addition to being a quality of consciousness, it has been argued that basic aspects of emotion are necessary for a level of consciousness in general. This basic emotional processing is thought to involve homeostatic regulation of the state of one's own body and a representation of "self" (Tsuchiya and Adolphs, 2007).

Two states of consciousness:

Awareness

The term 'awareness' is described as "having knowledge, and being conscious and cognizant." The term represents the state of mind at a particular moment of time, irrespective of whether that state of mind can be later recalled (Ghoneim and Mewaldt, 1990). Awareness implies both that the brain is aroused and that there are specific perceptual qualities of an experience (e.g. the redness of a rose). The modifier "explicit" distinguishes conscious awareness from other cognitive processes in the brain that are implicit to unconscious. For the sake of the present discussion, consciousness is defined as "explicit awareness." It is important to note that "explicit awareness" does not necessarily imply "explicit recall," as it often does in the discussion of awareness under anaesthesia.

The present review of the basic history and principles of the scientific investigation of consciousness, discusses proposed mechanisms of anaesthesia that explicitly consider the neural correlates of consciousness (NCC), and argues for an integrated approach to the study of consciousness and anaesthesia. In medical terminology, the term "awareness" has sometimes been regarded as meaning only consciousness during general anaesthesia (Osterman, 2001). In some cases, post traumatic stress disorder (PTSD) may arise after intraoperative awareness, which may lead to the patient to requiring counselling for an extended period. New research has been carried out to determine what people can remember after general anaesthesia, in an effort to more clearly understand anaesthesia awareness and help to protect patients from experiencing it. The causes of intraoperative awareness are, as yet, unknown and the problem may be multifactorial with 4 or more broad categories of plausible causes. It has been found that a genetic deficiency in one type of receptor for the inhibitory neurotransmitter γ-amino-butyric acid (receptors that contain the α5 subunit) confer resistance to the memory-blocking properties of the anaesthetic etomidate, which causes awareness during anaesthesia (Cheng *et al*., 2006). Polymorphisms of the γ-amino-butyric acid A receptor 5 gene (GABRA5) exist in the human genome, and there are at least 3 distinct messenger RNA isoforms in human adult and fetal brain tissue linked to awareness during anaesthesia (Kim *et al*., 1997).

Human studies have shown that the immobilizing dose of anaesthetic may vary by as much as 24% in populations with different genetic backgrounds. Thus, pharmacogenetics may be one factor contributing to intraoperative awareness (Ezri *et al*., 2007). The term "awareness during general anaesthesia" is almost universally accepted in both medical and legal circles, and its meaning is well understood. In 2001 Hameroff presented a paper entitled *Anaesthesia: the other side of consciousness*; subsequent papers illustrated that general anaesthesia is a direct road not only to the neural correlate, but also to the molecular mechanisms of consciousness. The term "awareness" is chosen because of its consistency with the current terminology used in anaesthesiology, i.e., awareness is typically regarded in contradistinction to anaesthesia.

Memory and recall

This describes a situation when patients can recall events postoperatively but were not necessarily conscious enough to responding to commands. The incidence of a state with both responses in various degrees is also possible.

3. A BRIEF HISTORY OF GENERAL ANAESTHESIA

Anaesthesia was first demonstrated successfully in 1846 at the Massachusetts General Hospital and over the following decade chloroform, ether, and nitrous oxide were administered as general anaesthetics (Bernard, 1875).

a) General anaesthesia

Unconsciousness has always been a fascinating topic and therefore it is no wonder that soon after the demon-

stration of the EEG in humans, the effects of anaesthetics on EEGs began to be studied. Since general anaesthesia is defined as a state of unconsciousness, it would logically follow that a patient under general anaesthesia cannot be aware, and the converse. If the brain is anaesthetized, consciousness ceases. General anaesthesia can be described as a (i) state (characterized by unconsciousness, analgesia, muscle relaxation, and depression of reflexes (Willenkin, 1990)), or a (ii) process (the administration of chemical agents to produce reversible unconsciousness and depression of reflex responses to afferent stimuli (Osterman, 2001)). General anaesthesia is sometimes referred to as a **"controlled coma",** and is characterized by four features: (1) the lack of motor response to instructions, (2) suppression of autonomic and skeletal responses to intraoperative stimuli such as incisions, (3) absence of retrospective awareness of pain, and (4) postoperative amnesia for surgical events such as conversations among the medical team.

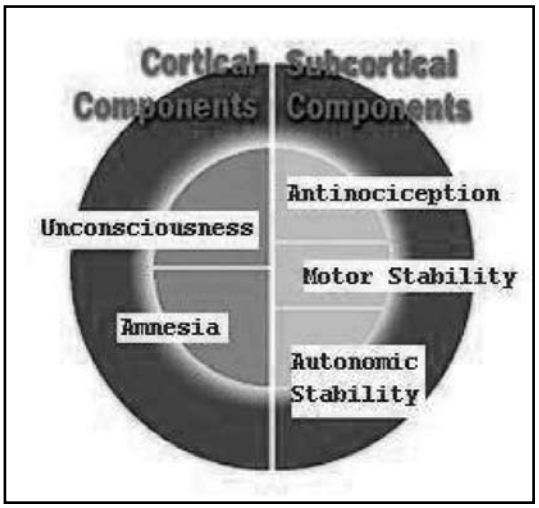

Fig. 1. The five components of general anaesthesia.

In modern medical practice, general anaesthesia is a state of total unconsciousness resulting from administration of general anaesthetic drugs (Fig.1) (Pesu, 2008). Anaesthetic drugs are drugs which induce a reversible loss of consciousness. These drugs are generally administered by an anaesthesia provider in order to induce and/or maintain general anaesthesia to facilitate surgery. General anaesthetics are drugs that: depress the function of cerebral cortex, and decrease awareness of the patient as the dose of the drug increases.

The specific physiological mechanism by which anaesthesia is achieved probably differs for each different class of anaesthetic agents. Of course, anaesthesia is a complex procedure and on occasion things go wrong. In cases of inadequate anaesthesia the patient may be aware of the surgery as it goes on. Preoperative sedation may reduce anxiety, and the analgesic administered as part of the "balanced" cocktail may reduce worry; but the muscle relaxant, also administered as part of "balanced" anaesthesia, prevents the patient from communicating that they are still awake until after the procedure is over. Fortunately, the incidence of surgical awareness is very low (well under 1%), and is most common in procedures such as Caesarean section, trauma surgery, and certain cardiac procedures, where the standard of care permits only a light plane of anaesthesia to begin with (Orser *et al.*,2008).

The clinical use of these diverse agents also led to a fundamental scientific question: What is the mechanism of general anaesthesia? Anaesthetics influence a wide variety of transmitter- and voltage-gated ion channels in the CNS:

- gama-aminobutyric acid (GABA) subtype A receptor (Eckenhoff *et al.*, 2002),
- nicotinic acetylcholine receptors (nAChRs),
- potassium channels, and
- AMPA subtype of the glutamate receptor (GluR).

Neuromuscular blocking drugs are capable of activating nicotinic ACh receptors. Several drugs widely used as part of general anaesthesia (anaesthetics and neuromuscular blocking drugs e.g. atracurium and cistracurium metabolite laudanosine, interact with nicotinic ACh receptors and are involved in chemical signalling in the brain (Fodale and Santamaria, 2003).

How does anaesthesia work?

We still do not know exactly how general anaesthesia works, but modern neuroscientific research has at least suggested a number of plausible hypotheses. The most commonly accepted theory is that general anaesthetics operate directly on the central nervous system to temporarily inhibit synaptic transmission (the chemical means by which neural impulses are transmitted between adjacent neurons). This results in a general loss of consciousness that affects sensory awareness in all modalities and at all body loci.

Beyond this general statement, one "non-specific" theory holds that anaesthetics impair the operation of the sodium pump, preventing depolarization of postsynaptic neurons. A more recent "dual-process model" suggests that anaesthetics simultaneously inhibit the actions of excitatory neurotransmitters such as glutamate and acetylcholine and enhance the actions of inhibitory neurotransmitters such as GABA and glycine (Eckenhoff and al., 2002).

Is there unconscious processing during anaesthesia?

By definition, adequately anesthetized patients rarely show any conscious recall or recognition of surgery. Nevertheless, there is some evidence that surgical events may be processed to some degree even by

adequately anaesthetized patients, resulting in the encoding of memory traces of experiences that can affect post surgical experiences, thoughts, and actions (Koch and Mormann, 2008). Prima facie evidence for information processing during general anaesthesia is provided by studies of classical conditioning in animals: conditioned fear responses can be acquired during anaesthesia, and displayed after recovery. This evidence is mitigated, however, by the empirical fact that conditioned responses can be established in almost any organism that has a nervous system, including decorticate animals. This primitive form of learning should not be confused with the higher cognitive processes involved in intelligent perception, memory, and thought.

Other evidence indicates that adequately anesthetized patients continue to show event-related potentials (ERPs) to auditory and tactile stimulation (ERPs are specific electrical responses of the brain to environmental stimuli). In fact, ERPs constitute one way in which the patient's status can be monitored during surgery. However, the ERP is very complex: for example, the first 10 milliseconds of the auditory ERP reflect brainstem activity, those arising bewteen 10 — 100 msec represent activity in the primary auditory cortex, and those observed after 100 msec represent activity in the cortical association areas. Only the early components of the ERP are clearly unaffected by anaesthetic agents (these are the only components routinely monitored during surgery); the later, perceptual-cognitive components exhibit dose-related suppression of activity. To date, there have been few studies regarding the later components of the cognitive ERP, such as the P300 response to the omission of an expected event, or the N400 response to semantic anomalies.

In the absence of definitive studies of cognitive ERPs, on-line evidence of complex mental activity comes primarily from studies using the "isolated forearm technique," in which a muscle relaxant is prevented from affecting one arm by means of a tourniquet (Thornton and Sharpe, 1998; Sániová, 1994). In some (but not all) cases, the patient retains the ability to make a motor response with the spared limb in accordance with instructions from the anaesthetist, but this is usually confined to the earliest stages of surgery, where the plane of anaesthesia is the lightest. However, most adequately anesthetized patients have no conscious recollection of having been given these instructions, or of responding to them.

Mechanism of the anaesthetic drugs

As early as 1847, von Bibra and Harless (1847) suggested that anaesthetics dissolve and remove lipids found in the brain. In 1875, Claude Bernard (1875) formulated the original "unitary hypothesis" of general anaesthesia, suggesting that all of these structurally and pharmacologically diverse agents have a final common mechanism. Around the turn of the 20th century, Meyer (1901) and Overton (1901) observed that the potency of volatile anaesthetics was correlated with their solubility in olive oil. The synthesis of these ideas led to the "lipid hypothesis" of general anaesthesia, i.e. anaesthetics act by non-specific perturbation of the lipids in the cell membranes of neural tissues. Variations on the lipid membrane hypothesis of general anaesthesia persisted late into the 20th century until Franks and Lieb (1997) demonstrated in 1984 that anaesthetics inhibit lipid-free preparations of the firefly enzyme, luciferase, in parallel with their hydrophobicity. From the time of this discovery, the specific actions of anaesthetics on protein substrates have been intensely investigated. Despite the potentially "promiscuous binding" of anaesthetics, the primary molecular focus has been ion channels. Ion channels serve a number of functions within the neuron and are the molecular mediators of the neurophysiology that forms the basis of consciousness. General anaesthetics affect a number of different neurotransmitter receptors, including gamma aminobutyric acid (GABA) type A, nicotinic acetylcholine, and glutamate receptors in the brain, as well as glycine receptors in the spinal cord (Eckenhoff *et al*., 2002; Fodale and Santamaria, 2003).

The central cholinergic system plays a major role in the regulation of cognitive functions; and it has been shown that inhibition of central nicotinic and muscarinic cholinergic receptors (nAChRs and mAChRs) contributes to learning and memory impairment and delirium (Perry *et al*.,1997).

Neuroanatomical structure

Neuroanatomical structures affected by general anaesthetics include the: thalamus, cuneus and precuneus, posterior cingulate cortex, orbitofrontal cortex, and right angular gyrus. The molecular, neuronal, and neurophysiologic effects of general anaesthetics have been extensively reviewed elsewhere (Fiset *et al*., 1999; Cavanna and Trimble, 2006).

Current Theories of General Anaesthesia

The anaesthetic cascade is a theory of how anaesthesia suppresses consciousness. The proposed "cascade" is as follows (John and Princhep, 2005): (1) Depression of the brainstem reduces the influences of the ascending reticular activating system on the thalamus and cortex. (2) Depression of the mesolimbic-dorsolateral prefrontal cortex interactions leads to blockade of memory storage. (3) Further depression of the ascending reticular activating system leads to hyperpolarization of GABAergic neurons in the nucleus reticularis of the thalamus, resulting in (4) blockade of thalamocortical reverberations and the associated gamma-oscillations which underlie perception. Functional uncoupling of parietal-frontal cortical activity leads to interruption of

cognition and finally reduced awareness, and increased activity in the frontal δ and θ bands.

The cascade is organized by first describing molecular actions of anaesthetics then linking these actions to neural correlates of consciousness such as thalamocortical resonance and gamma oscillations (greater than 40 Hz).These frameworks of consciousness and anaesthesia are not dependent on the depressive actions of anaesthetics, but instead focus on the disorganization of processes that bind information together (associating areas).

CONCLUSIONS

The concept of consciousness can be described in two main ways: (i) consciousness as experience and (ii) consciousness as the waking state. Consciousness is present in the waking state, and absent or low in the sleeping state.

The level of consciousness is related to the level of vigilance (James, 1892).

- States of consciousness are waking, drowsiness, sleeping, REM sleep and several altered states, such as coma, anaesthesia and hallucinations. States of consciousness are studied relative to the neural correlates of consciousness, such as the electroencephalogram (EEG), and the reticulo-thalamo-cortical system.
- The reticular formation in the upper brainstem regulates consciousness by the ascending reticular activating system (ARAS).
- The ARAS activates the thalamo-cortical system via the dorsal glutamatergic pathway and the ventral cholinergic pathway. The low level of consciousness experienced during sleep is induced by the GABA-ergic system located in the lower brainstem.

In 1947, Harvard anaesthesiologist Henry Knowles Beecher (1947) published a prescient article in Science entitled "*Anaesthesia's Second Power: Probing the Mind*." Nearly 60 years later, perhaps the time has come to actualize this "second power." The scientific pursuit of a better understanding of consciousness and general anaesthesia appear to have converged, suggesting the potential for an integrated science. The first power (influence of general anaesthesia on the mind) in clinical anaesthesia led to a revolution in the 19th century and continues to provide benefits to patients worldwide. Perhaps the second power of anaesthesia can contribute to another revolution, providing critical insights to the science of consciousness in the 21st century. The early decades of the twenty-first century will undoubtedly see great advances in our understanding of the neural correlates of consciousness. What is less certain is whether such empirical observations will bring us any closer to resolving what philosopher David Chalmers (2002) has called the 'Hard Problem,' that is, what is the true nature of subjectivity? We may be forced to admit that consciousness, like infinity and particle-wave duality concepts in quantum mechanics, is a property that cannot be understood intuitively. Consciousness may be one of the irreducible properties of the universe for which no further account is possible; consciousness is no simple thing, it is the complicated, sophisticated, interactive process of billions of neurons.

Lastly, it is a matter of no small significance that some minimum level of consciousness is both essential and perquisite for any understanding of consciousness. If consciousness is in fact a product of evolution and exists on a spectrum, then ultimately and frustratingly, a complete understanding of consciousness may always be just beyond our grasp, as it continually redefines itself as we continue to evolve.

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