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Acetylcholine in mind: a neurotransmitter correlate of consciousness?

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The cholinergic system is one of the most important modulatory neurotransmitter systems in the brain and controls activities that depend on selective attention, which are an essential component of conscious awareness. Psychopharmacological and pathological evidence supports the concept of a 'cholinergic component' of conscious awareness. Drugs that antagonize muscarinic receptors induce hallucinations and reduce the level of consciousness, while the nicotinic receptor is implicated as being involved in the mechanism of action of general (inhalational) anaesthetics. In degenerative diseases of the brain, alterations in consciousness are associated with regional deficits in the cholinergic system. In Alzheimer's disease (AD), there is a loss of explicit (more than implicit) memory and hypoactivity of cholinergic projections to the hippocampus and cortex, while the visual hallucinations experienced by subjects with Dementia with Lewy bodies (DLB) are associated with reductions in neocortical ACh-related activity. In Parkinson's disease, the additional loss of pedunculopontine cholinergic neurones, which control REM (rapid eye movement) sleep or dreaming, is likely to contribute to REM abnormalities, which also occur in DLB. Widespread basal-forebrain and rostral brainstem cholinergic pathways, which include converging projections to the thalamus, appear to be located strategically for generating and integrating conscious awareness. Alleviation of a range of cognitive and non-cognitive symptoms by drugs that modulate the cholinergic system, which are being developed for the treatment of AD and related disorders, could be caused by changes in consciousness.

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CONSCIOUSNESS is increasingly being considered in terms of neural correlates. In this context, diseases that affect human brain systems, and drugs that mimic or relieve symptoms, provide insights into mechanisms of consciousness. Jean Delacourt[1] has suggested that 'some positive psychotic syndromes, consisting essentially of aberrations of conscious experience, hallucinations, delusional beliefs may provide relatively vital leads'. One syndrome that is associated with psychosis is Dementia with Lewy bodies (DLB), which was recognized recently as being the second most prevalent degenerative dementing disorder in the elderly[2]. Core symptoms of DLB, such as visual hallucinations, fluctuating levels of conscious awareness and absence episodes, can be examined in terms of specific pathological and functional abnormalities. Extensive neocortical cholinergic-system deficits in hallucinating DLB individuals are consistent with the ability of muscarinic-receptor antagonists, such as scopolamine to induce similar types of visual hallucinations[3]. Therapy using drugs that modulate the cholinergic system (such as cholinesterase inhibitors) relieves both cognitive and neuropsychiatric symptoms, including hallucinations observed in AD and related disorders.

It has been suggested that general anaesthetics produce their effects via actions on both muscarinic and nicotinic receptors, which indicates that ACh might control not only the content of conscious awareness but also its level or intensity. Further insights into mechanisms that underlie consciousness have emerged from the neurophysiology of REM (rapid eye movement) sleep or dreaming, which is influenced by pedunculopontine cholinergic neurones that project to the reticular formation and thalamus. REM-sleep abnormalities that occur in DLB and PD might reflect pathology in this brainstem cholinergic nucleus. Specific actions of ACh could, thus, represent previously unrecognized neural correlates of consciousness that are involved in integrating and defining the boundaries of the conscious 'stream' of awareness.

Neural correlates of consciousness

Sommerhoff and MacDorman's definition of a primary level of consciousness as 'an awareness of one's

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surroundings, of the self, and of one's thoughts and feelings'[4] serves to identify a territory for neurobiological investigation. Neural correlates of consciousness are being sought at various levels, ranging from specific brain regions, which are examined using methods such as *in vivo* imaging, to single neuronal types (for example, thalamic reticular or cortical pyramidal neurones) and intracellular components such as microtubules. Two distinct components of conscious awareness have been identified[5], the first covers arousal–access–vigilance and the second covers mental experience–selective attention. Consciousness, when described as explicit, declarative or reflective, can be distinguished from implicit, non-reflective, subliminal or unconscious processes[6], although whether the latter 'automatic' processing is necessarily unconscious is not clear.

The original assumption by James, that the cerebral cortex is the essential locus of consciousness (see Ref. 7 for a review), was challenged by the discovery of the role of the brainstem reticular formation in the facilitation of cortical activation[8]. In the mid-1990s the focus of research shifted further to nonspecific intralaminar thalamic nuclei, in the search for one of the key integrative centres of consciousness[9,10]. Paré and Llinás[9] have concluded that the dorsal thalamus is the only structure, owing to its sufficiently extensive projections to the cerebral cortex from intralaminar nuclei, together with the integration of cortical inputs to the reticular nucleus from the cortex, that can generate synchronized oscillatory activity (see below) in distant groups of neurones that characterize both wakefulness and paradoxical, REM sleep. Bogen[10] has suggested that 'the quickest route to a better understanding of subjective awareness involves a more intensive study of the intralaminar nuclei'. However, Jones[11] has recently proposed that a matrix of cells that extend throughout the thalamus and project across wide areas of the cortex, is 'essential for the binding of multiple aspects of sensory experience into a single framework of consciousness'.

Electrophysiological indices of consciousness and ACh

The human electroencephalogram (EEG), which is measured using electrodes placed on the scalp surface, reflects ongoing rhythmic electrical activity generated by the brain. Such measures provide insight into cortical activation states, which are thought to be facilitated by key sub-cortical structures such as the thalamus and reticular activating system. Altered states of consciousness are reflected in characteristic EEG changes: different stages of sleep (REM-sleep versus non-REM-sleep patterns); confusional states and delirium (lower frequency EEG); and stupor or semicoma (for example, α coma, distinguished by the specific band frequency). An ACh-mediated component of EEG desynchronization was demonstrated in the 1950s (see Ref. 12 for a review).

Theories of arousal have recently been revised since the discovery of high-frequency (40 Hz), synchronized oscillation, which is thought to 'bind' cortical information coherently[13]. Yet ACh is still considered to be a key factor in the genesis of such rhythms: *in vitro* application of ACh induces fast, synchronized activity in hippocampal-slice preparations[14]. Hallucinogenic drugs that inhibit ACh-mediated transmission induce slow-wave EEG; more-extensive slowing is correlated with increased clouding of consciousness. Intoxication induced by scopolamine, a muscarinic-receptor antagonist, in clinical and experimental settings, results in behavioural and EEG manifestations of delirium that can be reversed with cholinesterase inhibitors such as physostigmine[15]. The presence of ACh-receptor antagonists in serum correlates with delirium in postoperative patients and in patients undergoing electroconvulsive therapy[16]. In AD, EEG slowing is generally reported and is more evident during REM sleep[17], probably because noradrenergic and serotonergic neurones are virtually silent during REM sleep, which unmasks forebrain cholinergic-neurone derangements. A recent analysis has indicated that the quantitative REM-sleep EEG is more useful than single-photon emission computerized tomography (SPECT) imaging in evaluating cerebral dysfunction in mild to moderate AD (Ref. 18).

A more specific electrophysiological measure of conscious attention is the event-related potential (ERP), which is a cerebral waveform generated in response to a novel stimulus (for example, sensory). One component of the ERP is the positive slow–late wave at approximately 300 ms (P300), which is considered to be a specific sign of conscious attending. As healthy subjects pass through the various stages of orthodox sleep this potential is gradually attenuated and disappears, but reappears in REM (paradoxical) sleep with a similar profile to that seen in the waking state. The cholinergic system has been implicated in the generation of this conscious attending potential. Studies in humans have demonstrated that P300 latency increases and that its amplitude is reduced with the administration of scopolamine, effects that are reversed by physostigmine[19]. These findings are consistent with animal studies showing that physostigmine alone increases P300 amplitude. Lesions of basal-forebrain cholinergic neurones result in delays in P300 latency and reductions in its amplitude. This effect is reversed with vagal-nerve implants, which restore P300 characteristics that correlate with the restoration of cortical levels of the enzyme, choline acetyltransferse[20].

Relevant cholinergic pathways

The cholinergic system might be the most important neuromodulatory (as opposed to executive) neurotransmitter system in the brain. It is distributed in a variety of different nuclei of which two groups (basal forebrain and pedunculopontine) have both extensive divergent projections and, in the cortex and thalamus (including reticular nucleus), also have convergent projections (Fig. 1). Cholinergic projections from the basal forebrain to the cortex and thalamus are considered to be essential for controlling selective attention, and the fact that 90% of brainstem projections to the thalamus are cholinergic[21] is of particular interest in view of the importance of the thalamus in conscious awareness (see above).

According to Mesulam[22] the extent of nucleus-basalis cholinergic projections to the human cortex indicates that 'this pathway is likely to constitute the single most substantial regulatory afferent system of the cerebral cortex'. On the basis of the observation that cortical activation is maintained during REM sleep in the absence of monoaminergic-neurone activity (for example, noradrenergic and serotonergic) but in the presence of

continued firing of nucleus-basalis cholinergic neurones, Buzsaki[23] concluded 'it appears that the ascending cholinergic system alone is capable of keeping the neocortex in its operative mode'. However, the excitatory glutamatergic input to the nucleus basalis that arises in the brainstem[24], together with the major thalamocortical glutamatergic projections, indicate that the combined actions of ACh and glutamate are essential in this respect. The consensus view on the role of cortical cholinergic projections is that they control selective attention. As Delacour[1] has speculated that selective attention and consciousness overlap, and Baars[25] has highlighted the importance of selective attention in the 'theatre' metaphor of consciousness, the two processes might share a common neural basis. While attentional processes can occur at the non conscious–implicit level, conscious awareness, which represents only a fraction of cerebral activity at any time, clearly involves a selection process. Current theories of the role of cortical ACh include the possibility that it affects discriminatory processes; increases signal–noise ratios; modulates the efficiency of cortical processing of sensory and association information; controls the reception and evaluation of stimuli for their level of significance; modifies cortical responsiveness in terms of the relevance and novelty; and confines the contents of the conscious stream[3,26–32]. Basal-forebrain cholinergic neurones project not only to all cortical areas but also to select thalamic nuclei, including the reticular nucleus[33], which has been implicated in selective attention[34].

Combined retrograde labelling and choline acetyltransferase immunohistochemical studies have established that 85–95% of brainstem afferents to most thalamic nuclei, which include specific-relay, nonspecific and reticular nuclei, originate in the rostral brainstem where pedunculopontine cholinergic nuclei and lateral dorsal tegmental nuclei are maximally developed[21]. These inputs are excitatory and exert their effects both directly, via fast nicotinic-receptor mediated and slower muscarinic-receptor mediated depolarization, and also indirectly via hyperpolarization of GABAergic (inhibitory) reticular neurones[35]. Co-activation of brainstem and basal-forebrain cholinergic neurones that project rostrally, which occurs in both wakefulness and REM sleep, provides the thalamus and cortex with a role in integrative modulation of distant neurones (synchronization) that could represent a component mechanism of conscious awareness.

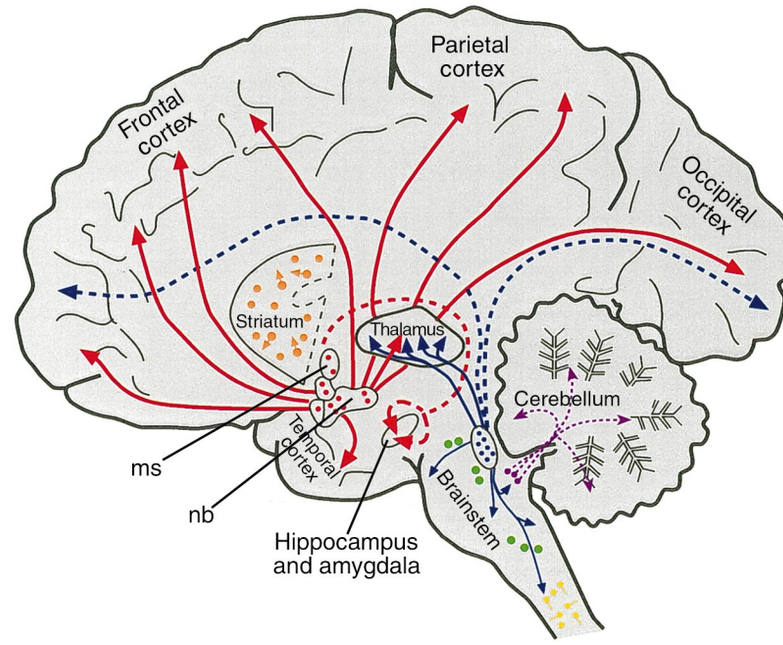

Fig. 1. ***Cholinergic systems in the human brain.*** *Two major pathways project widely to different brain areas: basal-forebrain cholinergic neurons [red, including the nucleus basalis (nb) and medial septal nucleus (ms)] and pedunculopontine–lateral dorsal tegmental neurons (blue). Other cholinergic neurons include striatal interneurons (orange), cranial-nerve nuclei (green circles), vestibular nuclei (purple); and spinal-cord preganglionic and motoneurons (yellow). A group of cholinergic neurons in the thalamic paracentral nucleus (not shown), thought to project to striatum and visual cortex, has recently been identified in macaque brain[101]. The habenula–interpeduncular pathway is also not shown.*

Cholinergic neuropathology in mental disorders

Abnormalities in the cholinergic system have been consistently identified in disorders that affect conscious awareness, which include AD, PD and DLB (reviewed in Ref. 3). The pathology in the nucleus of Meynert, which includes neurofibrillary tangles, Lewy bodies or neurone loss, together with deficits in the cholinergic system in the cortex and hippocampus, detected at autopsy, and more recently, using chemical imaging[36], has been linked to cognitive impairment and memory impairment, and might also relate to alterations in consciousness experienced by patients with these diseases. In AD, explicit memory is affected more than implicit memory: the latter involves learning of which the patient is unaware. Loss of explicit memory occurs due to early degeneration in the medial-temporal-lobe memory systems, which are primarily, if not exclusively, involved in declarative memory. Implicit memory for novel patterns and cognitive or motor-skill learning have, however, been reported to be unimpaired[37]. This suggests that it is not so much information storage and retrieval *per se* that are primarily compromised in AD, and that 'cholinergic correlates' of cognitive impairment might instead be correlates of the degree of unawareness experienced by the patient. Lack of awareness of cognitive impairment is common in AD, more so than in vascular dementia[38], and is correlated with the degree of cognitive impairment[39]. Brainstem pedunculopontine cholinergic neurones are reportedly unaffected in AD (Ref. 40) or modestly reduced (by 30%)[41]. The latter finding is not only consistent with the presence of intracellular neurofibrillary tangles but also with the presence of 'ghost' tangles in this nucleus (where the cell body is no longer identifiable).

In AD, different pathological manifestations, such as cortical and subcortical β-amyloidosis (which results in plaque formation), abnormal tau (which results in the development of tangles and dystrophic neurites), neuronal and synapse loss, and various transmitter deficits, leave clinical-neuropathological correlations open to a variety of interpretations. Deficits in cholinergic neurotransmission are unlikely to account for the full spectrum of cognitive and non-cognitive symptoms. The situation is less complex in PD and DLB, in which cortical neurofibrillary tangles are much rarer or absent, and β amyloid plaques are not invariant. In these disorders, neocortical deficits in ACh-mediated neurotransmission are generally greater than in AD and yet cognitive impairments not as severe.

Patients with DLB and, to a lesser extent, those with PD experience hallucinations that are primarily visual and frequently persistent[2]. In DLB, neocortical ACh-related activities (especially in the temporal and

Fig. 2. ***Belladonna* (Atropa belladonna *or deadly nightshade*).** *This plant, together with other closely related species such as henbane, mandrake and datura, which contain atropine and scopolamine, has been used for centuries to induce hallucinations.* Atropa mandragora *(mandrake) was also used by the ancient Romans to abolish pain and induce sleep during surgical procedures.*

parietal cortex) are lower in patients with hallucinations[42]. While this identifies a cortical 'cholinergic correlate' of hallucinogenesis in DLB, abnormalities in REM sleep (below) could also implicate the pathology of pedunculopontine neurones, with intrusions of REM into the waking state. The integrated visual images of people or animals that are encountered by hallucinating patients are similar to those experienced following ingestion of muscarinic-receptor antagonists, such as scopolamine or atropine, in ritualistic, recreational or medical situations (Fig. 2; see Ref. 3 for a review). In both PD with dementia and AD, hallucinations are attenuated by the cholinesterase inhibitors physostigmine, tacrine or metrifonate[43–45]. In PD, antimuscarinic agents affect cognitive shifting (which is assessed by card-sorting tests) and memory performance. As in AD, memory impairment in PD is apparent in tasks that test explicit-memory function as opposed to implicit-memory function[46]. Both non-demented and demented PD patients perform normally in automatic or implicit mental tasks (for example, word or picture-fragment identification). In PD, a loss of pedunculopontine neurones (around 50%) occurs[41], which could be responsible for sleep abnormalities (see below).

Another feature of DLB that is distinct from AD is the prominent fluctuation in symptoms, which include the level of consciousness with episodes of reduced awareness of surroundings[2]. Patients, while not unconscious or asleep, can, for seconds, minutes or hours, cease to respond to external stimuli. These absence episodes are not epileptic in origin nor are they obviously the result of cardiovascular deficiencies. Reductions in the number of cholinergic projections to the thalamic reticular nucleus have been identified in DLB that do not occur to the same extent as in AD or PD (Ref. 47), despite the loss of pedunculopontine neurones in the latter. Whether dysfunction of the cholinergic system accounts for these changes in the level of conscious awareness remains to be established, although a recently identified mechanism of anaesthesia that involves the cholinergic system supports this concept (see below).

Box 1. The discovery of ACh

Rapid eye movement (REM) sleep or dreaming sleep is triggered by firing and release of ACh from pedunculopontine cholinergic neurones. In 1921, Otto Loewi, the German-born pharmacologist and physician, discovered ACh. The method he used to do this was inspired by a dream[a].

> I awoke, turned on the light, and jotted down a few notes on a tiny slip of thin paper. Then I fell asleep again. It occurred to me at six o'clock in the morning that during the night I had written down something most important, but I was unable to decipher the scrawl… The next night, at three o'clock, the idea returned. It was the design of an experiment to determine whether or not the hypothesis of chemical transmission that I had uttered seventeen years ago was correct. I got up immediately, went to the laboratory, and performed a single experiment on a frog heart according to the nocturnal design.

Loewi transferred Ringer solution from a frog heart, which was stimulated by the vagus nerve, to another isolated frog heart in which contractions then became slowed, as if its vagus had been stimulated. These results proved that the vagal nerve does not influence the heart directly, but via the release of a specific chemicals. Loewi shared the Nobel prize for physiology and medicine in 1936 for this discovery, together with Dale and Dudley, who were able to identify the reactive substance in the fluid as ACh.

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Pathophysiology of REM-sleep patterns

Resemblances between wakefulness and paradoxical, REM-sleep physiology are likely to provide important clues as to the neurobiological mechanisms of consciousness[1,9]. One of the most important neurophysiological events that triggers REM sleep or dreaming is the firing of cholinergic neurones in the pedunculopontine nuclei. It is a striking coincidence that the neurotransmitter that activates dreaming mechanisms was originally discovered as the result of a dream (Box 1).

The hypothesis that REM or dreaming involves the cholinergic system was first formulated by Jouvet and Hernandez-Péon (see Ref. 48 for a review) over ten years before a cholinergic hypothesis was applied to the cognitive impairment that occurs in dementia. Distinct patterns of firing in mesopontine cholinergic neurones precede and coincide with REM-sleep onset. A REM-sleep induction zone in the dorsolateral mesopontine tegmentum receives 40% of its input from these neurones. Carbachol- or glutamate-elicited excitation of brainstem pedunculopontine tegmental cholinergic cells induces REM sleep, and AChE inhibitors, such as tacrine, decrease REM-sleep latency and increase REM-sleep duration. Neurotoxic lesions of this region (produced using kainic acid) result in reductions in the duration of REM sleep in the cat that parallel the severity of cholinergic- but not noradrenergic-neurone loss. Muscarinic-receptor antagonists, such as atropine or the blockade of the vesicular ACh transporter by vesamicol[49] also decrease REM-sleep activity by increasing its latency or decreasing its density and duration, or both.

TABLE 1. Rapid eye movement (REM) sleep abnormalities in degenerative diseases of the human brain

Disease	Abnormality	Potential ACh-related correlates	Refs
Parkinson's disease	Reduced REM latency and duration	REM abnormalities could depend on relative pathology of PPN and NbM neurones, or pathology of noradrenergic and serotonergic neurones that inhibit PPN cholinergic neurones	50–52
	REM behaviour disorder, in some instances preceding movement disorder	Loss of PPN cholinergic neurones that control muscle atonia (descending projections to spinal cord) and REM generation or abnormalities in afferent projections (for example, GABAergic) to these neurones	51,53,54
Dementia with Lewy bodies	REM behaviour disorder	Similar to Parkinson's disease	55–57
Alzheimer's disease	Decreased REM duration and density, increased REM latency REM behaviour disorder	Basal forebrain, as opposed to PPN, ACh-related neuropathology might be primarily implicated	53,58–60

Abbreviations: NbM, nucleus basalis of Meynert; PPN, pedunculopontine.

In degenerative brain diseases, loss of neurones or histological features, such as neurofibrillary tangles or Lewy bodies in brainstem serotonergic, noradrenergic or cholinergic neurones, could interfere with REM sleep and in turn contribute to disturbances in consciousness, such as hallucinations or delusions. In AD, reductions in REM (Table 1) have been hypothesized to lead to or contribute to progressive loss of memory and other cognitive skills[61]. Decreased REM sleep correlates with the cognitive decline seen in AD (Ref. 58) and there are reductions in both REM-sleep duration and also in REM-sleep density, which distinguish AD from depression. There is, however, one case report of abundant REM sleep in AD (Ref. 62), which highlights the need to relate REM patterns to the relative involvement of different brainstem nuclei in individual cases. REM-sleep-behaviour disorder (RBD), which describes the loss of muscle atonia that can occur during REM-sleep associated with movement, often violent, during dream mentation, has been reported to precede clinical symptoms of AD in one case[63]. In this case, there was a loss of locus-coeruleus neurones, which inhibit pedunculopontine cholinergic neurones, in conjunction with, surprisingly, elevated numbers of mesopontine cholinergic neurones.

REM-sleep disturbances have been reported more frequently in PD than in AD and include reductions in REM-sleep latency and also RBD, which are relieved by selegeline or L-dopa (Table 1). A striking observation was made by Schenck[53] that RBD preceded clinical Parkinsonism (by over ten years on average) in 38% of 29 older male PD patients. Hallucinating PD patients experience significantly decreased REM-sleep duration (3 min versus 50 min) and percentage REM-sleep–total-sleep time (5% versus 20%) compared with non-hallucinating PD patients[52]. Hypnapompic or hypnagogic hallucinations (which can occur normally on waking or falling asleep) are thought to consist of brief intrusions of REM into the waking state. Hallucinations in PD or DLB could, therefore, have a similar but, owing to brainstem pathology, extended basis. REM-sleep-behaviour disorder has been identified in isolated cases of DLB and incidental (or otherwise asymptomatic) Lewy-body disease (Table 1), and the latter is associated with loss of locus-coeruleus and substantia-nigra neurones. Substantia-nigra pathology is interesting in view of the importance of dopamine-sensitive GABAergic pathways, which project from the output nuclei of the basal ganglia, in controlling pedunculopontine cholinergic neurones[64]. A syndrome that was recently identified clinically as 'RBD Dementia' is thought to represent a form of DLB where patients have greater attention–concentration and perceptual-organization deficits than those seen in AD patients (Ref. 65).

Pathology of pedunculopontine cholinergic or dorsolateral tegmental neurones has been consistently described in terms of neurone loss in PD (on average 50%), although tangles or Lewy bodies are present in these cells in AD and DLB. Locus-coeruleus neurone loss is more common and usually extensive (up to 70%) in all of these disorders, whereas substantia-nigra neurone loss is extensive in PD, moderate in DLB and rare in AD, and raphé-nucleus neurone loss occurs in PD. It will be important in the future to determine the effects of therapy using drugs that affect the cholinergic system, for example, cholinesterase inhibitors and muscarinic- or nicotinic-receptor agonists, on REM-sleep patterns in patients with these disorders. If REM-sleep abnormalities or RBD relate to cholinergic-neurone pathology, they could be attenuated by therapy. However, restoring normal sleep patterns (which has been reported to occur with tacrine[66]), or REM sleep might not always be beneficial. There is a report of two AD patients who have experienced Aricept-induced nightmares[67].

Clinical responses to drug therapy

The low frequency of identifiable synaptic-membrane differentiations on choline acetyltransferase immunostained axon terminals in the rat cortex and hippocampus[68], indicates that the dominant mode of cortical ACh-mediated transmission might be 'diffuse', as opposed to point synaptic. Moreover, reversal of behavioural deficits in basal-forebrain cholinergic-neurone-lesioned rats, following implantation of ACh-secreting cells, indicates that impulse-dependent regulated synaptic release of ACh might not be necessary for functional recovery[69]. These characteristics might provide an explanation for functional correlates of systemically administered drugs that affect the cholinergic system in patients with AD and related disorders.

TABLE 2. Response to drug therapy in Alzheimer's disease[a]

Drug[b]	Cognitive effects	Non-cognitive effects	Refs
Physostigmine	Non-dose-dependent improvement (ADAS-COG)	Decreased agitation Non-dose-dependent improvement in CGIC	70[c] 71[c]
Tacrine	Improvement in attentional as opposed to mnemonic function (CANTAB)	Decreased delusions and apathy; reduced disinhibition	43 72
	No difference between drug and placebo (MMSE)	Improvement in ADAS non-cognitive items (for example, delusions, co-operation)	73[c] 74[c]
	Improvement in 8 out of 11 ADAS cognitive items (for example, word recall, comprehension, language production, orientation)		75
Donepezil	Dose-dependent improvement (ADAS-COG and MMSE)	Dose-dependent improvement (CIBIC)	76[c] 77[c]
Metrifonate	Improvement (ADAS-COG and MMSE)	Decreased hallucinations	45 78[c]
Xanomeline		Reduced delusions, hallucinations and behavioural disturbances	79[c]
Nicotine	Improvement in attention but not memory		80

[a]Reports from 1993 onwards; for a recent review, see Ref. 81.
[b]All cholinesterase inhibitors except xanomeline, a muscarinic-receptor agonist, and nicotine, a nicotinic-receptor agonist.
[c]Placebo controlled.
Abbreviations: ADAS-COG, Alzheimer's Disease Assessment Scale (cognitive subscale); CANTAB, Cambridge Neuropsychological Test Automated Battery; CGIC, Clinician Global Impression of Change; MMSE, Mini Mental-State Exam.

Since the introduction of the cholinesterase inhibitors tacrine (Cognex) and, more recently, donepezil (Aricept) and rivastigmine (Exelon), for the treatment of AD, clinical outcome (Table 2) has generally been assessed in terms of the recovery of cognitive function [using, for example, the Alzheimer's Disease Assesment Scale (cognitive subscale) or Mini Mental-State Exam (MMSE)]. Cognitive functions that improve include word recall, word recognition, orientation, language production, comprehension, word finding and command following. Symptomatic improvements are generally modest and confined to a minority of patients, although whether such therapy provides additional protection against further cognitive decline is still being evaluated. Neuropsychiatric or non-cognitive functions have been assessed to a lesser extent but appear to be equally if not more amenable to therapy with cholinesterase inhibitors[81]. Physostygmine, tacrine and metrifonate have been reported to decrease psychosis (hallucinations and delusion), agitation, apathy, anxiety, disinhibition, pacing and aberrant motor behaviour, and to improve cooperation in AD (Table 2). Such evidence, that enhancing the activity of cholinergic neurones attenuates a broad spectrum of cognitive and non-cognitive functions, is consistent with a general role for ACh in selective attention, and suggests that ACh is involved centrally in the mechanism of conscious awareness.

The mechanism of action of anaesthetics: involvement of ACh

The identity of the neurochemical systems that are involved in consciousness can be inferred from the mechanisms of action of general anaesthetics, which induce loss of consciousness and awareness of sensory stimuli. The theories behind the mechanism(s) of action of general (volatile) anaesthetics have been complicated by the diversity of chemical agents used. In the 1980s, the fluidizing or disordering effects of anaesthetics on membrane lipids were the main focus of attention and related to their ability to disrupt neuronal excitability. However, it soon became evident that the disordering of membrane lipids was, in effect, small and did not correlate with the relative potencies of different anaesthetic agents. The research focus then shifted to proteins, in particular voltage-gated ion channels. Although Na^+, K^+ and Ca^{2+} channels are all affected by anaesthetics, the doses required are usually supratherapeutic. More recently ligand-gated ion channels have been intensively studied, including, in particular, glutamate NMDA, $GABA_A$, glycine and nicotinic receptors (see Ref. 82 for a review).

Although there is still no consensus on whether all volatile anaesthetics act via a single, identical mechanism, nor any consensus on whether there is a specific receptor involved, evidence for the involvement of the cholinergic system, particularly nicotinic receptors, is growing. In the *Torpedo* electric organ and mammalian myotubes, nicotinic receptors have been implicated as a sensitive target for many years (Table 3). Agents such as isoflurane, butanol and chloroform increase channel opening rate and increase rates of fast and slow desensitization at concentrations similar to those reported for anaesthetic actions on the $GABA_A$-receptor channel. More recently, it has been reported that the subtype of nicotinic receptor found in the CNS ($\alpha4\beta2$) is more sensitive than the muscle subtype, with IC_{50} values for halothane or isoflurane being 10–35 times higher in muscle than in the CNS, and that the $\alpha4\beta2$ receptor is more-sensitive to isoflurane than the most sensitive $GABA_A$ receptor or glycine receptor previously reported. The extreme sensitivity

TABLE 3. ACh-related mechanisms of anaesthesia

ACh-related component	Effects of volatile anaesthetics (at clinically relevant concentrations)	Refs
Muscle nicotinic receptors (*Torpedo* electric organ or mammalian myotubes)	Isoflurane, butanol and chloroform increase channel opening, and both fast and slow desensitization	83–86
CNS nicotinic-receptor subtype $\alpha4\beta2$	Thiopental inhibits receptor-mediated current	87
	More sensitive to halothane or isoflurane than the muscle subtype of nicotinic receptor	88
	More potently inhibited by isoflurane than $GABA_A$ receptors or agonists at the glycine site	89
Muscarinic M_1 receptor	Halothane inhibits Ca^{2+}-dependent Cl^- currents in M_1-receptor transfected oocytes	90
High-affinity choline uptake	Inhibited by halothane in cortical synaptosomes	91,92
Nicotine-elicited release of dopamine	Inhibited in the striatum by halothane	93
ACh release	Reduced in the cat medial pontine reticular formation by halothane	92
	Reduced in the rat cerebral cortex by isoflurane	94

of the neuronal nicotinic receptor to such compounds suggests that its inhibition is relevant, at least in conjunction with effects on other members of this superfamily of fast neurotransmitter-gated receptors, to the loss of conscious awareness that they produce.

Other evidence that links ACh to anaesthesia (Table 3) includes halothane inhibition of the mechanism of high-affinity choline uptake into rat cortical synaptosomes; decreased nicotine-elicited release of striatal neurotransmitters such as dopamine; and inhibition by halothane of the muscarinic-receptor induced Ca^{2+} dependent Cl^- current. Historically, muscarinic-receptor antagonists pre-dated inhalational agents in anaesthesia. Naturally occurring alkaloids, such as atropine and hyoscine (scopolamine), have been used in anaesthesia for over a century and records suggest this application could date back to early Roman times. Scopolamine induces 'twilight sleep' in which the patient is awake but unaware and subsequently amnesic for the event. Although the cholinergic hypothesis of geriatric memory impairment was partly created on the basis of results obtained from experimental models of scopolamine-induced memory loss, muscarinic-receptor block induces a more-global disruption, which might be as relevant to understanding the pathophysiology of dementia. Tacrine, the first prescription drug for AD, has been used since the 1960s as a ventilatory stimulant and to promote the recovery of consciousness following anaesthesia, an effect that is similar to that produced by physostigmine, though of greater duration and with fewer side effects.

Neuroimaging

Monitoring cholinergic-neurone activities *in vivo* provides new opportunities for the examination of clinical correlates of pathological or drug-induced changes in the cholinergic system, including alterations in conscious awareness. Chemical markers of the cholinergic system are progressively being developed for PET or SPECT imaging of the human brain *in vivo*. The vesicular ACh transporter has been monitored using iodobenzovesamicol and it has been shown that reductions in its binding capacity correlate with cognitive impairment in AD patients. In PD patients, this reduction of binding capacity is more pronounced in demented than non-demented subjects[36]. An inhibitor of AChE, *N*-methyl-4-piperidyl acetate has been used to demonstrate consistent reductions in the levels of AChE in AD, which are more prominent in the parietal and temporal cortices than in the frontal, occipital and sensorimotor cortices[95]. Iodinated quinuclidinyl benzilate {[^{123}I]QNB} binding, measured using SPECT, is reduced in advanced but not moderate AD cases[96]. Using iododexetimide, a muscarinic-receptor antagonist that might be more specific for the M_2 receptor subtype, it has been demonstrated, in one SPECT study, that a reduction in muscarinic-receptor levels in the temporal and parietal cortices is apparent in mild probable AD (Ref. 97). Administration of the muscarinic-receptor antagonist, scopolamine, decreased [^{123}I]QNB binding in controls but had the opposite effect in AD patients, which indicates a differential receptor sensitivity in the disease[98]. Reductions in [^{11}C]nicotine-binding in temporal cortex of AD patients, which is reversed by tacrine, have been reported in PET studies[99]. Other potential imaging markers of the cholinergic system are in development and alterations in cerebral perfusion that result from treatment with drugs that affect this system are also being investigated.

Concluding remarks

Although the subject of transmitters or other neural correlates of consciousness might be considered to be academic, in relation to major diseases of the brain, disturbance of conscious awareness is a major predictor of personal and social dysfunction. It is over 30 years since ACh release in the cerebral cortex was originally correlated with consciousness and shown to increase during waking and dreaming compared with non-dreaming sleep. Since then, different cholinergic pathways in the brain have been characterized, and their involvement in brain diseases that affect cognition and consciousness have been reported. As drugs emerge for the treatment of AD and ligands for imaging the cholinergic system *in vivo* proliferate, new opportunities arise that allow the examination of the role of cholinergic systems in the human brain. Beyond objective measures of cognition, memory and behaviour, it will be valuable to explore subjective experiences that involve conscious awareness, including such components as hallucinogenesis, levels of consciousness, and REM sleep or dreaming. The physiological, pharmacological and pathological

data reviewed in this article are consistent with the concept that the action of ACh in the cortex and thalamus is essential for the maintenance of the normal experience of conscious awareness. In the words of Alexander Karczmar[12], 'no behaviour is a one-transmitter affair… yet, frequently the cholinergic system constitutes the significant correlate'. The way in which ACh might contribute to generating the integrated, coherent experience of conscious awareness remains to be established. During preparation of this article, a novel hypothesis, that ACh enhances the activity of specific circuits involved in conscious awareness by promoting the interaction between microtubule-associated protein 2 (MAP2) and microtubules, was published on the basis of data from parallel-distribution studies of MAP2 and postsynaptic muscarinic receptors in the cortex[100]. Interactions between ACh and other neurotransmitters, in particular glutamate and GABA, which control basal-forebrain and pedunculopontine cholinergic neurones, are likely to provide further insights into cholinergic correlates of consciousness. Acetylcholine will no doubt need to compete with other candidate neurochemical correlates of consciousness, as it does with other neurotransmitters in determining the physiological response of receptive neurones.

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Erratum

Homeostatic plasticity in neuronal networks: the more things change, the more they stay the same, by Gina G. Turrigiano, Vol. 21, pp. 221–227.

In Fig. 3B, some mathematical symbols were omitted. It should show negative values on the x-axis, and read 'Reduced activity ÷ 2.68' and 'Enhanced activity × 1.58'.

We apologize to the author and readers for this error.

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