Acetylcholine and Hallucinations: Disease-Related Compared to Drug-Induced Alterations in Human Consciousness

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Newly proposed criteria for Lewy body dementia include alterations in consciousness. Lewy body dementia is also associated with a disturbance in cholinergic transmission; neocortical cholinergic deficits in this disorder are more extensive than in Alzheimer's disease and are correlated with symptoms commonly associated with delirium, such as visual hallucinations. The traditional view that derangements of the basal forebrain cholinergic system in Alzheimer's disease relate specifically to memory impairment is assessed in terms of a more general role for cortical acetylcholine in consciousness. This extends the concept that cortical acetylcholine enhances neuronal signal to noise ratio. It is suggested that muscarinic receptor activation in the cortex is involved in confining the contents of the discrete self-reported conscious "stream." In the absence of cortical acetylcholine, currently irrelevant intrinsic and sensory information, which is constantly processed in parallel at the subconscious level, enters conscious awareness. This is consistent with the ability of anti-muscarinic drugs administered medically, recreationally, or ritualistically to induce visual hallucinations and other perceptual disturbances. The hypothesis is explored through comparisons between muscarinic and nicotinic receptor psychopharmacology and between the pathology of the basal forebrain as opposed to pedunculopontine cholinergic systems in different diseases of the human brain affecting consciousness and cognition. The paradoxical effects of muscarinic receptor blockade to induce hallucinations and of REM sleep-associated cholinergic activation of the thalamus to induce dreaming may be related to the differential distribution and activity of muscarinic receptor subtypes or to the differing responses of intrinsic GABA neurons in cortex and thalamus. © 1995 Academic Press, Inc.

INTRODUCTION

As the subject of consciousness enters the domain of respectable neuroscience, there is as yet no consensus on a single or unitary definition. This may

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reflect the personal, subjective nature of consciousness or that, like memory for example (Baddeley, 1988), it is "not a unitary function but rather an alliance of interacting systems serving different functions." A simplistic although useful subdivision, which may be applicable to disorders of the human brain, can be made between arousal and content. The arousal component—analagous in mechanistic terms to "volume" control—refers to the intensity of generalized mental activity, ranging from unconscious though subconscious to conscious states. The content component—analagous perhaps to "channel" selection—comprises the single, self-reported stream of current awareness—being conscious of something in particular such as sensory input, memories, emotion, thoughts, self, and so on. The latter is only a fraction of mental activity at one time.

Although disorders of cognition such as Alzheimer's or Parkinson's disease are not commonly considered from the point of view of consciousness, the DSM III criteria of 1980 included such categories as delusional disorder (distinct from schizophrenia). Recently proposed operational clinical criteria for Lewy body dementia (Perry, Irving, Blessed, Fairbairn, & Perry, 1990b; McKeith, Perry, Fairbairn, Jabeen, & Perry, 1992) include alterations in consciousness such as hallucinations and periodic clouding or even loss of consciousness. Symptoms in this disorder fluctuate and are not obviously associated with morphological changes (Lewy body density, for example), although hallucinations relate to the extent of the cortical cholinergic deficit (Perry et al., 1990a). New insights into the nature of consciousness may emerge from considering the role of cerebral transmitters such as acetylcholine in disease and there are intriguing parallels between symptoms associated with the neurochemical pathology of Lewy body dementia and alterations in consciousness induced in normal individuals by cholinergic compounds which antagonize muscarinic receptors.

Lewy Body Dementia

A rare disorder originally described in the 1960s as Diffuse Lewy body disease, in which Lewy bodies (the hallmark of Parkinson's disease) are evident in the cortex, has recently emerged as a distinct clinical and neuropathological entity. It is reported to be the second most common form of degenerative dementia in old age after Alzheimer's disease (for a recent review, see Hansen & Galasko, 1992). Clinical criteria, established on retrospective review of cases examined at autopsy (Perry et al., 1990b, McKeith et al., 1992), include fluctuating cognitive impairment affecting both memory and higher cortical functions (such as language, visuospatial ability, praxis, or reasoning skills). The fluctuation is pronounced with both episodic confusion and lucid intervals (as in delirium) which persists for months or even years (unlike delirium). Altered consciousness includes the occurrence of mainly visual or occasionally auditory hallucinations, accompanied in some

instances by secondary paranoid delusions. Transient loss of consciousness and mild, spontaneous extrapyramidal features are apparent in some cases, the latter being exaggerated by standard neuroleptic treatment. Although Alzheimer's original case description included paranoid delusions and, later in the course of the disease, auditory hallucinations, misidentification, and misperception, these symptoms occur in only 5–30% of cases of AD but in up to 70% of cases of LBD. Typically, the hallucinated patient with LBD reports seeing integrated images of people or animals which appear real at the time.

Neuropathologically, neither cortical Lewy bodies nor senile plaques (the latter evident in most but not all cases) clearly correlate with the clinical symptoms of LBD such as hallucinations (Table 1). The fluctuating nature of the symptomatology suggests that the root cause may not be at the morphological level—neuron loss, for example, is irreversible. In contrast, neurochemical evidence suggests that some of the mental symptoms of LBD are associated with extensive *neocortical* cholinergic deficits, marked by the loss of the enzyme synthesizing acetylcholine—choline acetyltransferase (Perry et al., 1990a, 1993). These are more pronounced in Lewy body dementia compared with Alzheimer's disease, where *archicortical* (for example, hippocampal) cholinergic deficits are the most extensive. This is consistent with impairments in memory in Alzheimer's. In a recent neurochemical analysis of LBD patients, cholinergic enzyme activity in temporal and parietal cortex was reduced to below 20% of the normal in hallucinating patients compared with around 50% in those not experiencing hallucinations (Perry et al., 1993). Although other neurotransmitter disturbances also occur, for example in cortical 5-HT or somatostatin and in striatal dopaminergic activities, in LBD these are not so obviously associated with hallucinations (Table 1). The relative sparing of the 5-HT system may lead to a monoaminergic:cholinergic imbalance which, through depleted acetylcholine, gives rise to hypermonoaminergic activity. Interestingly, hallucinations, similar to those evident in LBD, i.e., primarily visual consisting of integral images of people or animals, are associated with high doses of levodopa in Parkinson's disease and disappear with reducing dosage. These hallucinations may be due to a relative hypocholinergic activity since they are more common in diffuse Lewy body disease cases that present with dementia as opposed to extrapyramidal symptoms (Byrne, Lennox, Lowe, & Godwin, 1989), presumably reflecting a relative sparing of cortical cholinergic activity in the latter.

Although dementia occurs in a proportion of Parkinson patients, more subtle cognitive impairments are frequently noted, especially those relating to frontal lobe function. These include difficulties in cognitive shifting which can be monitored in the Wisconsin card sorting test. This test requires the subject to detect and respond to specific changes in the required sorting strategy apparent against a background of closely related but, as far as the strategy is concerned, irrelevant information. Impaired capacity is exacerbated in Par-

TABLE I
Neurochemical Activities in Hallucinating versus Non-hallucinating
Patients with Lewy Body Dementia

	Hallucinating		Not hallucinating	
Age	79 ± 6	(9)	81 ± 6	(5)
Mental test score	14 ± 10	(8)	21 ± 10	(4)
Neocortical senile plaques	14 ± 10	(9)	13 ± 8	(5)
Entorhinal Lewy bodies	57 ± 39	(9)	43 ± 31	(5)
Substantia nigra neurons	350 ± 171	(9)	283 ± 111	(5)
Meynert (Ch4) neurons	33 ± 11	(3)	53 ± 15	(3)
Locus coeruleus neurons	24 ± 22	(8)	26 ± 12	(6)
Striatal (caudate) transmitters				
Dopamine	73 ± 65	(5)	66 ± 67	(4)
Homovanillic acid	161 ± 36	(5)	223 ± 31	(4)
5-hydroxytryptamine (5-HT)	15 ± 10	(5)	12 ± 5	(4)
5-hydroxyindoleacetic acid (5-HIAA)	30 ± 21	(5)	33 ± 15	(4)
Choline acetyltransferase (ChAT)	124 ± 114	(4)	222 ± 135	(4)
Cortical (temporal lobe) transmitters				
Cholinergic				
Choline acetyltransferase	*1.5 ± 1.6	(6)	4.0 ± 1.7	(5)
Muscarinic receptor binding	201 ± 37	(5)	192 ± 29	(5)
Nicotinic receptor binding	3.7 ± 2.2	(6)	5.2 ± 1.5	(5)
Monoaminergic				
5-HIAA	17.3 ± 11.2	(6)	9.7 ± 6.0	(5)
HVA	24.6 ± 14.5	(5)	13.2 ± 9.1	(5)
5-HT: receptor	33.1 ± 20.1	(4)	16.4 ± 2.4	(4)
5-HIAA: ChAT ratio	**9.3 ± 3.5	(5)	3.1 ± 2.2	(5)
Neuropeptides				
Somatostatin	457 ± 146	(5)	525 ± 208	(5)
CRF	552 ± 202	(5)	395 ± 134	(5)
Vasopressin (arginine)	10.7 ± 1.7	(5)	9.5 ± 0.8	(5)

Note. Units are as follows: Mental test scores (Blessed) optimum = 37, plaques per mm^2, Lewy bodies per cm^2, neuron counts as nucleoli containing cells per coronal section of entire nucleus, monoamines and metabolites pmol/mg protein, choline acetyltransferase nmol/h/mg protein, muscarinic receptor assessed by [³H]N methyl scopolamine binding and nicotinic as [³H]nicotine binding as fmol/mg protein, 5-HT₂ receptor assessed by [³H]ketanserin binding as fmol/mg tissue, neuropeptides pmol/mg protein.

*** Differences between the two groups (Student's *t* test) significant ($p < .05$ and $p < .02$); data are mean ± *SD*.

kinson patients treated with anticholinergic drugs to improve extrapyramidal control (Van Spaendonck, Berger, Horstink, Buytenhuijs, & Cools, 1993). In a recent autopsy survey, cholinergic activities in Parkinson's disease were more attenuated in frontal than other cortical areas (Perry et al., 1993). In Alzheimer's and Parkinson's disease, cognitive, especially retrieval-dependent, functions are more adversely affected by scopolamine than in age-matched controls (Sunderland, Tariot, & Newhouse, 1988; Dubois et al.,

1987). The range of cognitive impairments in Alzheimer's, Parkinson's, and Lewy body dementia so far correlated with declining cholinergic function, includes memory (primarily explicit), cognitive shifting, and sensory perception. Anatomically, these impairments can be related to the cortical area most affected. There may, however, be a unitary function of the transmitter that accounts for common features of the symptoms.

Role of Acetylcholine in the Cerebral Cortex

Insights into the role of acetylcholine in human cognition have arisen more from the effects of anticholinergic drugs such as scopolamine on normal individuals than from observations on diseases with complex pathology such as Alzheimer's. Sahakian (1988) has indicated that "the most parsimonious account of the effects of scopolamine might be to suggest that it affects discrimination processes, whether these involve vigilance, selective attention, consolidation or retrieval." Based on the effects of this antimuscarinic drug on human cognition, Drachman and Sahakian (1979) originally proposed that normal cholinergic transmission produces optimal signal to trace detectability or "noise" ratio. Extending this idea on the basis of further observations on drug effects on human cognition, Warburton (1981) proposed that the release of acetylcholine in the cortex increases the size of postsynaptic potentials and increases the probability of their being distinguished from background cortical activity. More recently, Rusted and Warburton (1988) provided evidence that scopolamine decreases the ability to focus on one of two channels, consistent with acetylcholine improving signal to noise ratio. Since the mid-1970s it has been attractive to link the consequences of experimentally deranged cholinergic activity to those occurring in Alzheimer's disease with its prominent cortical particularly archicortical cholinergic deficits. The "cholinergic hypothesis" so generated has not yet been verified on the basis of the outcome of cholinergic treatment in patients.

In a recent review of acetylcholine and memory, Hasselmo and Bower (1993) discussed neurophysiological evidence that acetylcholine may "set the dynamics of cortical networks to the learning mode." Muscarinic blockade prevents acquisition as opposed to recall effects, that are more prominent in discriminative learning when multiple or irrelevant cues are presented, or in tasks with discriminating patterns presented at low as opposed to normal contrast (Hasselmo & Bower, 1993). This important concept can clearly be extended well beyond the realms of memory. Hallucinations occurring as a result of impaired cholinergic transmission may be due to an inability to suppress intrinsic cortical activity during perception.

Returning to the neurophysiological level, Metherate, Tremblay, and Dykes (1987) have reported that iontophoretic application of acetylcholine increased firing in 20–30% of somatosensory neurons, whereas the response of 92% of neurons to visual stimuli was altered by acetylcholine. Although

a minority of neurons altered their resting potential to acetylcholine alone, the majority (75%) altered in response to combined exposure to both acetylcholine and glutamate concomitantly. These authors propose that acetylcholine permits enhancement of previously less effective synaptic connections.

These diverse experimental approaches have lead physiologists and psychologists to remarkably similar conclusions regarding the role of acetylcholine in the cortex. The signal produced by acetylcholine (at least at muscarinic receptors) appears to be more of a facilitator than initiator and this contributes to distinguishing the dominant from closely competing (or near similarly active) neural networks or pathways. In terms of behavior, it would be reasonable to deduce that selective attentional mechanisms are involved. A logical, if only hypothetical, extension of this scenario to subjective consciousness is that cortical acetylcholine is involved in selecting the most currently relevant information into the conscious stream from the massive parallel information processing that occurs at the subconscious level. The transmitter would, by suppressing irrelevant material, confine the content of self-reported mental activity.

In diseases of the human brain where the cortical cholinergic input is diminished, the major problem—according to this hypothesis—would be the failure to focus on the most relevant information and to maintain an appropriate conscious stream of awareness, with the intrusion of currently irrelevant information from the subconscious into this uppermost level of consciousness. Three neuropsychiatric features related to cholinergic derangement—the working memory impairment of Alzheimer's, cognitive shifting deficit of Parkinson's, and visual hallucinations of Lewy body dementia are, in conjunction with the brain region affected, explicable on this common basis. Although acetylcholine is often considered to be specifically involved in memory mechanisms, it is worth noting that some forms of implicit memory (which in contrast to explicit memory do not depend on conscious awareness) are intact in Alzheimer's disease despite cholinergic dysfunction (Heindel, Salmon, Schultz, Walicke, & Butters, 1989). The cholinergic derangement in AD and other disorders could then be viewed as disturbances in conscious awareness due to increased noise to signal ratio. A further extension of the hypothesis is that drugs enhancing cortical acetylcholine should limit the conscious stream, providing improved focus, whereas cholinergic blockade should have the reverse effect.

Cholinergic Drugs and Hallucinogenesis

The word hallucination is derived from the Latin, alucinari, meaning to wander and the Greek word, alvein, meaning distraught. This highlights the affective dichotomy between the negative experience of the mentally ill and the positive experience sought after in the use of hallucinogenic drugs for recreational or ritualistic (sacred or otherwise) purposes. In the context of

the hypothesis that cortical acetylcholine suppresses currently irrelevant sub-conscious mental activity, individuals using anticholinergics for pleasure presumably regard a voluntary anticholinergic experience as interesting in terms of exploring the contents of the subconscious as they are released into conscious awareness. By contrast, the involuntary disease situation is gener-ally (although not always) regarded as unpleasant and there may be scope for reducing negative reactions with appropriate support.

Among the wide range of hallucinogenic chemicals employed by man in his search for "enlightening" experiences or "expansions" in conscious-ness are those acting on the 5-HT (e.g., LSD), cathecholamine (mescaline, cocaine), GABA (muscimol, β-carbolines), glutamate (PCP), and cholinergic (e.g., scopolamine or atropine) systems. In a fascinating account of hallucino-genic drugs entitled "Plants of the Gods," Schultes and Hofman (1992) noted the presence of antimuscarinic agents (tropane alkaloids such as sco-polamine and atropine) in the majority of plants with identified hallucino-genic chemicals. There were fewer plants with hallucinogenic compounds specifically active on other transmitter systems. One of the best replicated findings in modern behavioral pharmacology may be that muscarinic block-ade with scopolamine impairs memory performance. However, one of the most widely described religious or magical experiences dating back to an-cient times is the alteration of consciousness with induction of hallucinations (primarily visual) by members of the Solanaceae family of plants (bella-donna, henbane, or Datura) which contain scopolamine, atropine, and other closely related tropane alkaloids.

Foremost in most lists of commonly prescribed medical drugs which acci-dentally induce delirium are those with anticholinergic activity. The phenom-enon is so widespread that it has been suggested (Thienhaus et al., 1992) that safe psychopharmacotherapy should include monitoring, by muscarinic receptor assay, of serum anticholinergic activities. The young and old are particularly vulnerable to iatrogenic reactions to anticholinergic medication. This is consistent with lower cholinergic activities in the developing cortex and senescent compared with the mature adult human cortex (Perry et al., 1992). Other reports on anticholinergic drug-induced alterations in con-sciousness (Table 2) range from psychedelic substance abuse in adolescents, adverse reactions to opthalmic or anti-motion sickness medication in normal individuals, and applications of atropine prophylactically in organophos-phate toxicity. Perhaps the most extraordinary example is the criminal use of anticholinergic drugs in Datura extracts to induce not only amnesia but also submissive behavior or "obedience in victims," which are said to be mediated by cholinergic regions of the amygdala (Ardila & Moreno, 1991). This example of anticholinergic drugs rendering individuals more vulnerable to suggestion and leaving them with no memory of their externally controlled actions is reminiscent of hypnosis. It has even been suggested that "zom-bies" in Haiti are maintained in a state of confusion and virtual slavery

TABLE 2

Examples of Hallucinations Induced by Anticholinergic Chemicals

Experimentally administered high doses of scopolamine in normal volunteers	Integrated, realistic hallucinations with familiar objects and faces	Ketchum et al. (1973)
Side effects of scopolamine (anti-motion sickness) transdermal medication	Adolescents hallucinating and unable to recognize relatives	Wilkinson (1987) Holland (1992)
Intravenous atropine in bradycardia	Intense visual hallucinations on eye closure	Fisher (1991)
Local application of scopolamine or atropine eyedrops in opthalmic practice	Prolonged anticholinergic delirium in normal adults	Tune et al. (1992)
Jimson "loco" weed (Datura) abuse in adolescents	26/29 cases admitted to hospital experiencing hallucinations, most commonly visual	Shervette et al. (1979)
Accidental Datura innoxia (angel's trumpet) toxicity	Inadvertent ingestion of plant root followed by delirium, including visual hallucinations	Hanna et al. (1992)
Atropine in U.S. helicopter pilots self-injected prophylactically against organophosphate poisoning	Visual disturbances recorded in conjunction with decreased cognitive skills	Caldwell et al. (1992)
Scopolamine-adulterated cocaine sniffing	Confusion and hallucinations in adult male drug abusers (absence of cocaine in preparation)	Nogue et al. (1991)

Note. Only a few, mostly recent reports are cited. An extensive literature on alterations in consciousness, including visual hallucinations, exists in relation to anticholinergic drug-induced delirium and (dating back to early times) ritualistic use of anticholinergics.

through the use of Datura stramonium (Davis, 1988). Hypnosis, as an expanded state of consciousness, may well have a cholinergic component.

The nature of hallucinatory experiences resulting from muscarinic blockade (Table 2) is generally visual and some descriptions are remarkably similar to those provided by patients with Lewy body dementia. For example, among the 26 of 29 adolescents hospitalized as a result of recreational ingestion of Jimson weed (Datura stramonium), which contains both atropine and scopolamine, visual hallucinations were most common. These included "insects on walls," "being chased by sharks," and "bicycles outside the fourth storey window" (Shervette et al., 1979). An elderly man mistaking angel's trumpet (Datura innoxia) for horseradish was "unable to recognize family members and picking at imaginary objects in the air" after ingesting the root (Hanna et al., 1992). Patients treated with atropine for bradycardia saw animals, motor cars, street scenes, country scenes, dead relatives, sea shells, sports scenes, "hundreds of marching British soldiers," and much more

(Fischer, 1991). Many of these experiences are enhanced during eye closure and relieved by visual input. In this respect they may resemble hypnagogic or hypnopompic hallucinations experienced by many normal people on falling asleep or emerging from sleep. Hallucinations resulting from sensory conditioning or deprivation induced experimentally are also similar in content and are enhanced by scopolamine (Warburton et al., 1985). A condition known as pereidolias, discerning images such as faces or animals in wallpaper, curtains, or clouds, is also common in delirium and is reported in patients with Lewy body dementia and some with Alzheimer's disease, where it is referred to as a misidentification syndrome.

The hallucinogenic effects of muscarinic cholinergic receptor blockade are highlighted in this discussion because of the close similarity to the experiences reported by patients with Lewy body dementia. The literature on mnemonic effects of the transmitter is far more extensive and no doubt different psychological foci would reveal cholinergic mechanisms in a range of cognitive functions. The hypothesis that cortical muscarinic mechanisms are involved in the transference of selected items of information from the vast potential of parallel, subconscious experiences to the momentarily restricted space of human conscious awareness is consistent with the experiences both with anticholinergic drugs and disease induced visual hallucinations. As to whether muscarinic or other cholinergic agonists may be therapeutically relevant to hallucinations in dementia, there is a preliminary report that delusions in Alzheimer's disease (including in one case hallucinations) are ameliorated by physostygmine (Cummings et al., 1993).

Contributions of Different Cholinergic Pathways to Altered States of Consciousness

Any interpretation of systemically administered anticholinergic drug effects is complicated by the many different cholinergic pathways in the brain which could be affected. Although muscarinic receptors are distributed in a decreasing rostral to caudal gradient in the brain with highest densities in forebrain systems, some (particularly non-M_1 subtypes) are also present in caudal regions (Monferini, 1992). There is no a priori reason to suppose than antimuscarinic hallucinogenesis is primarily a cortical as opposed to subcortical (or perhaps both cortical and subcortical) phenomenon. In contrast to the major M_1 muscarinic receptor subtype, nicotinic receptors—at least the predominant CNS form comprizing $\alpha_4\beta_2$ subunits (which have the greatest affinity for agonists such as acetylcholine, nicotine, cytisine or methylcarbamylcholine) are concentrated more caudally, particularly in the thalamic targets of the pedunculopontine-lateral dorsal tegmental cholinergic nuclei. Nicotinic anatagonists, such as mecamylamine, are not however reported to induce hallucinations.

Cholinergic cell groups projecting to diverse areas in mammalian brain

have recently been divided into eight divisions, Ch1–Ch8 (Mesulam, 1988; Semba and Fibiger, 1989). Ch1 and 2, the medial septal nuclei and diagonal band of Broca project primarily to the hippocampus. Ch3, the nucleus of the horizontal band of Broca projects to the olfactory bulb and Ch4, the nucleus of Meynert to the amygdala and cortex, particularly to limbic and paralimbic as opposed to sensory areas, with additional minor projections from Ch4 to select thalamic (reticular and mediodorsal) nuclei, striatum and the interpeduncular nucleus. The principal target areas of Ch1–4 have relatively high muscarinic and low nicotinic receptors. This contrasts with Ch5–6 which project to areas with a high density of nicotinic and relatively low muscarinic (especially M_1) sites. Ch5 in the pedunculopontine area of the brainstem projects to all thalamic nuclei and Ch6 in the laterodorsal tegmentum to select thalamic nuclei. There are also minor projections from Ch5 and 6 to the cerebral cortex, superior colliculus and lateral hypothalamus Ch5 innervating medial prefrontal cortex, lateral septum, diagonal band, and also raphé nuclei.

Cholinergic elements of the nucleus basalis of Meynert may represent a telencephalic extension of the brainstem isodendritic reticular core. This concept of a dual cholinergic reticular activating system is consistent with the arousal and content components of consciousness. The brainstem nuclei could comprise the "quantitative" or arousal component and the forebrain nuclei the "qualitative" or content component. Ch4, 5, and 6 are said to be particularly extensive in primate brain and, based on choline acetyltransferase immunocytochemistry in the human brain, Mesulam et al. (1992) noted that all cortical areas and cell layers contain cholinergic axons and terminals and that the cholinergic innervation is likely to constitute the single most massive regulatory afferent system of the cerebral cortex. The vast number of cortical cholinergic projections, especially in limbic and paralimbic areas have been described as "truly impressive" (Mesulam et al., 1992).

In addition to these projection systems there are also intrinsic cholinergic systems in the caudate-putamen. Around 1% of local circuit neurons in ventral striatal regions such as nucleus accumbens are said to contain the highest level of cholinergic enzyme activities in the entire brain. Intrinsic cholinergic neurons have also been identified in rodent but not primate cerebral cortex— a disparity that sounds a cautionary note for extrapolations based on the results of anatomical and pharmacological manipulations of rodent brain to the function of the human brain and the subject of consciousness.

McCormick (1989) has noted that whereas acetylcholine is purely excitatory in the cerebral cortex (where both GABA and glutamate containing intrinsic neurones are stimulated), in the thalamus, nicotinic interactions may be excitatory, whereas muscarinic activation mediates a decrease in k^+ conductance so inhibiting local circuit GABA neurons. This paradoxical effect of acetylcholine in inhibiting subcortical but exciting cortical GABA neurons, via muscarinic action, indicates that whereas the inhibitory effects of

GABA are enhanced in the cortex by basal forebrain projections they are suppressed in subcortical areas innervated by brainstem cholinergic projections. In terms of the present cholinergic "consciousness" hypothesis, cortical acetylcholine could, through enhancing inhibitory effects of GABA, confine the contents of conscious awareness. Through disinhibition in subcortical areas such as thalamus it could have the opposite effect—as indeed occurs with pedunculopontine cholinergic neuron activation during REM sleep. An alternative explanation for the paradoxical effects of atropine or scopolamine to induce hallucinations and of cholinergic activation of the thalamus to induce dreaming may be the selectivity of the drugs for muscarinic receptor subtypes. Among cloned muscarinic receptors expressed in cell models, subtypes m_1, m_3, and m_4 have a higher affinity for atropine than m_2 (Buckley et al., 1989)—the latter being a low proportion of the cortical and high proportion of the thalamic muscarinic receptor subtypes. In contrast to m_1, m_2 receptors inhibit acetylcholine release and this is likely to account for differences in the synaptic action of acetylcholine.

The tendency for the predominant CNS muscarinic subtype (M_1) and nicotinic subtype ($\alpha_4\beta_2$) to be distributed in a reciprocal fashion in the brain raises further questions about the role of these different cholinergic receptor types and whether the actions of the two major cholinergic projecting systems in the brainstem and forebrain can be distinguished on this basis. Like muscarinic antagonists, nicotinic antagonists such as mecamylamine also impair memory performance in animals and man (Levin, 1992; Newhouse et al., 1992), although agonists such as nicotine are generally considered to improve performance in tasks assessing attention as opposed to encoding. For example, Rusted and Eaton-Williams (1991) noted that nicotine improved recall in scopolamine-treated normal individuals on supraspan (30) as opposed to short (10) word lists. In patients with Alzheimer's disease, subcutaneous nicotine (up to 0.8 mg) improved sustained visual attention and reaction time but not auditory or visual memory (Jones et al., 1992). These authors incidentally noted attentional impairments, in addition to mnemonic deficits, in Alzheimer patients compared with controls. The high density of nicotinic receptors in thalamic nuclei such as lateral geniculate in human brain, compared with most other brain areas, especially cortex, is consistent with a role for nicotinic cholinergic transmission in optimizing attention by stimulating thalamic neurons to relay sensory input information to the cortex.

The nicotinic receptor is a relatively simple cationic (Na^+ and Ca^{2+}) channel, the opening of which leads to rapid depolarization, followed by desensitization. This contrasts with the slower onset and longer lasting G-protein coupled second messenger generation provided by activation of the majority of muscarinic receptor subtypes. A simplistic view of brainstem cholinergic projections activating generalized arousal mechanisms via the predominant action on nicotinic receptors could contrast with selective attentional mecha-

nisms via predominantly muscarinic mechanisms. This provides further potential counterparts of the activity and content components of human consciousness. Whereas responses to subconscious mental activities are extremely rapid, registration at the conscious awareness level takes considerably longer. A good example is the near instant response of the runner to the starter's gun but delay in his reporting hearing the signal.

Basal forebrain cholinergic pathways have been implicated in a broad range of human brain disorders associated with dementia (reviewed Perry, 1988). These include in addition to Alzheimer's, Parkinson's, and Lewy body disease, also Down's syndrome, progressive supranuclear palsy, Creutzfeldt Jakob disease, olivopontocerebellar atrophy, and alcoholic dementia. Neurochemical reductions in cortical cholinergic enzymes and/or loss of neurons from the Meynert nucleus are apparent in all of these diseases. The system is spared in Huntington's chorea, multiple sclerosis, motor neuron disease, depression, and schizophrenia. Whether there are clinical features common to the diseases involving, as opposed to sparing, this pathway is difficult to assess given the complex additional neuropathology or functional disturbances in the various disorders. Nevertheless such clinical–pathological correlative data as exist indicate that forebrain cholinergic pathology is associated with cognitive impairments similar to those presently considered in terms of conscious awareness.

Brainstem cholinergic neurons have only recently been investigated neuropathologically in diseases of the human brain. Numbers are reduced in Parkinson's disease and progressive supranuclear palsy (reviewed in Steckler et al., 1994) and remain to be examined in Lewy body dementia. Hallucinations are not noted in PSNP, suggesting as do the neurochemical data, that their anatomical origin in Lewy body dementia is not in the brainstem. It is conceivable that fluctuations in cognitive function or periodic episodes of loss of consciousness—aspects of the arousal component of consciousness—evident in Lewy body dementia relate to neuropathology of this region. Neither are consistent features of Alzheimer's disease in which the Ch5/6 cholinergic neurons are not diminished in number. The normality of REM sleep in Alzheimer's disease, despite disturbances in overall sleep pattern (Bliwse et al., 1989) is consistent with the integrity of these neurons in this disease (Woolf et al., 1989).

Comparisons between Lewy Body Dementia, Schizophrenia, and REM Sleep

Investigation of hallucinory experiences in dementing disorders such as Lewy body dementia naturally leads to comparison with the most prevalent human disorder associated with hallucinations—schizophrenia. By all accounts the hallucinatory experience of schizophrenia is much more complex than that in Lewy body dementia, involving predominantly auditory as op-

posed to visual hallucinations and a high degree of thought disorder and personal involvement. Although most recent neuropathological analyses in schizophrenia have focussed on atrophic changes in the temporal lobe, there is one report of an increased number of pedunculopontine NADPH-positive cholinergic neurons (Karson et al., 1991). This could reflect an aberration in developmentally induced neuronal death. It has been linked to a possible exacerbation of REM type dream mechanisms in the waking state so accounting for the hallucinations of this disorder. The hallucinations in schizophrenia may bear a closer resemblance to dream experiences than do those in Lewy body dementia where the individual is generally more an observer of hallucinatory visions than a participant in a subjective narrative and delusions are more a consequence of the hallucination.

The implication of brainstem pathology in schizophrenia is still tenuous. However discussion of the possible role of acetylcholine in consciousness would be incomplete without reference to the function of this transmitter in promoting REM sleep (reviewed, Hobson, 1990 and 1992). In the 1960s crystals of carbachol (a joint muscarinic-nicotinic agonist) inserted into the medial forebrain, midbrain, pons, or medulla elicited REM sleep in cats. Similar effects were reported with individual applications of bethanecol (muscarinic) and nicotine (nicotinic) agonists. Physostigmine, increasing levels of acetylcholine, or arecoline (a muscarinic agonist) are known to decrease REM latency and increase REM density and duration in normal volunteers (Jewett and Norton, 1986; Valazquez-Moctezuma et al., 1990). The peribrachial cholinoceptive REM triggering zone, receiving cholinergic terminals from the pedunculopontine neurons is devoid of m_1 but high in the m_3 muscarinic receptor molecular subtype (Monferini, 1992) and in nicotinic (nicotine) binding (Perry et al., 1989). It is likely that the different receptor responses—rapid depolarization and excitation via the nicotinic cationic channel and a later, longer lasting activity dependent on G protein coupled muscarinic induced second messenger responses—are interactive in governing cortically projecting neurons of the thalamus (Curro Dossi et al., 1991). Both in animals such as cats and in man pontine lesions abolish REM sleep (Lavie et al., 1984). Webster and Jones (1988) have shown that excitotoxic lesions in experimental animals in the brainstem reducing choline acetyltransferase by 60% diminish ponto-geniculo-occipital waves (which herald and accompany REM sleep) by 70%. Steriade et al. (1990) have demonstrated the complexity and heterogeneity of peribrachial and lateral dorsal tegmental neurons related to REM sleep in chronically implanted cats with four classes of neurons being activated prior to PGO waves, one class discharging during REM and one class after PGO. Whether all or only some of these neurons are cholinergic and if and how they are governed by noradrenergic and 5-HT neurons which, in contrast to cholinergic neurons, cease firing at the onset of REM remains to be determined. Nevertheless brainstem

cholinergic neuronal activation in initiating dreaming is obviously associated with an altered hallucinatory conscious experience.

Cholinergic Systems in Depression

Although connections between the REM hallucinoid state and schizophrenia are still only speculative, alterations in REM sleep—specifically increased latency, intensity and duration—are well documented in depression and are reversed by antidepressant medication; indeed endogenous depression is reported to improve with REM sleep deprivation (Vogel et al., 1990). Considerably before the 'cholinergic hypothesis' of cognitive impairment in Alzheimer's disease, it had been suggested that depression is associated with a predominance of cholinergic and mania with predominant monoaminergic activity. Thus cholinesterase inhibitors induce anergy, lethargy and dysphoria whereas cholinergic antagonists can induce mania (although they are not antidepressant). There are several inconsistencies: cortical choline acetyltransferase is not reduced in depressive illness; depression can coexist with Alzheimer's disease (which involves cholinergic hypoactivity); and (in contrast to cortical cholinergic activities which decline) the incidence of depression increases in old age. These may be reconciled in terms of abnormalities in the monoaminergic-cholinergic transmitter balance due to hypomonoaminergic activity.

The REM abnormalities in depression implicate a direct or indirect cholinergic dysfunction in the pedunculopontine cholinergic pathway. In view of the high density of nicotinic receptors on target (e.g., thalamic) areas of this pathway, it is intriguing to note that smoking is more prevalent in patients with depression compared with the normal and vice versa that depression is more prevalent in smokers than non smokers. Nicotine (tobacco) withdrawal is said to mimic early depression and may induce depression in those with a history of depression (reviewed Newhouse & Hughes, 1991; Glassman, 1993). Equally remarkable are the statistics that 60% of schizophrenic patients smoke and that their total tobacco consumption and intensity of smoking is notably higher than in "normal" smokers. There may be a pharmacological reason for this since nicotine promotes release of dopamine so perhaps offsetting the adverse effects of neuroleptic blockade on dopaminergic transmission. Nicotine induces an increase in receptor numbers (in contrast to almost all other transmitter receptors which are down-regulated by agonist action)—presumably as a result of desensitization. In the context of the hypercholinergic hypothesis of depression, the predeliction for tobacco may be an attempt to diminish excessive nicotinic receptor function. This possibility is not consistent with current trends in Alzheimer's disease therapy to stimulate cognitive function by reversing disease-related reductions in cortical nicotinic receptors through nicotine administration.

In the present context of acetylcholine and human consciousness, it could be argued that emotional disturbances are not relevant. And yet the contents of conscious awareness are radically altered in depressive illness, in terms of the intrusion of negative value judgments.

Toward a Wider Pathological and Psychopharmacological Cholinergic Perspective

A simplistic transmitter hypothesis of consciousness is not intended in this discussion. Instead, the proposed role of cortical acetylcholine in controlling conscious awareness could provide a more holistic basis for cholinergic investigations of human brain disorders. The application of cholinergic medication could also be viewed in a broader context. Cholinergic drugs (both muscarinic and nicotinic) are currently being developed and tested in Alzheimer's disease with a view to treating memory disorder. Clinical outcome has not generally been dramatic with the exception of subgroups of patients who do respond substantially to cholinesterase inhibition. These subgroups are likely to include patients with Lewy body dementia, in which intrinsic neuronal pathology in the cortex is not as severe as in Alzheimer's (Perry et al., 1993). In one clinical trial of the anticholinesterase tacrine (Eagger et al., 1991), responders initially coming to autopsy were neuropathologically identified by the presence of cortical Lewy bodies and neurochemically be extremely low neocortical cholinergic activities (Perry et al., 1994). Future evaluation of cholinergic therapy may benefit from assessment of a range of symptoms, including hallucinations and other subjectively reported alterations in consciousness. In addition targetting therapy selectively to the cortex may be of particular importance in view of the paradoxical effects of acetylcholine on GABA neurons and differential distributions of muscarinic receptor subtypes in cortical and subcortical regions such as thalamus. Cholinesterase inhibitors like tacrine increase acetylcholine throughout the brain and direct enhancement of cortical function may be countered by contradictory effects relayed through the thalamus from the brainstem.

Neuropathological or neurochemical analysis of postmortem tissue and brain scanning of patients with dementia could usefully be extended to measurements of both cortical and subcortical regions and correlations with a broader range of clinical symptoms which include disturbances in consciousness. Since Lewy bodies have been identified in psychiatric as opposed to normal "controls" employed in dementia or Parkinson's disease studies (Perry et al., 1990c), subgroups of patients with psychiatric syndromes such as schizophrenia or paraphrenia may have Lewy body disease. In a recent autopsy survey of schizophrenic patients Lewy bodies were identified in 2 of 17 cases (Perry RH, unpublished observation).

In terms of neurotransmitter function, the comparison made here for acetylcholine between mental disorders affecting consciousness and pharmaco-

logical manipulations extends those previously made for 5-HT or glutamate based on the similarity between the LSD or PCP drug experiences and schizophrenic disease. The release of suppressed information by drugs specifically interacting with the 5-HT$_2$ receptor subtype has obvious parallels with the effects of anticholinergic drugs. In evolutionary terms, it is interesting to note that the relative density of cholinergic input to the cerebral cortex (assessed on the basis of the activity of cholinergic enzymes such as choline acetyltransferase) is lower in the human compared to non human (e.g., rodent) brain. The expansion of the human cortex is reflected in a relative increase in the number of intrinsic (presumably mainly GABA and glutamate) neurons compared to the cholinergic innervation. Based on the present hypothesis on acetylcholine and consciousness, the expansion of conscious awareness in man in terms of contents and the ability to hold information in the conscious stream unrelated to external events, is likely to be associated with the emerging dominance of intrinsic over input (such as the cholinergic) systems in the normal human brain. Further exploration of the neurochemical pathology of the disordered human brain is likely to contribute to unraveling the mystery of consciousness.

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