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A Possible Role for Cholinergic Neurons of the Basal Forebrain and Pontomesencephalon in Consciousness

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Excitation at widely dispersed loci in the cerebral cortex may represent a neural correlate of consciousness. Accordingly, each unique combination of excited neurons would determine the content of a conscious moment. This conceptualization would be strengthened if we could identify what orchestrates the various combinations of excited neurons. In the present paper, cholinergic afferents to the cerebral cortex are hypothesized to enhance activity at specific cortical circuits and determine the content of a conscious moment by activating certain combinations of postsynaptic sites in select cortical modules. It is proposed that these selections are enabled by learning-related restructuring that simultaneously adjusts the cytoskeletal matrix at specific constellations of postsynaptic sites giving all a similar geometry. The underlying mechanism of conscious awareness hypothetically involves cholinergic mediation of linkages between microtubules and microtubule-associated protein-2 (MAP-2). The first reason for proposing this mechanism is that previous studies indicate cognitive-related changes in MAP-2 occur in cholinoceptive cells within discrete cortical modules. These cortical modules are found throughout the cerebral cortex, measure 1–2 mm^2, and contain approximately 10^3–10^4 cholinoceptive cells that are enriched with MAP-2. The subsectors of the hippocampus may function similarly to cortical modules. The second reason for proposing the current mechanism is that the MAP-2 rich cells throughout the cerebral cortex correspond almost exactly with the cortical cells containing muscarinic receptors. Many of these cholinoceptive, MAP-2 rich cells are large pyramidal cell types, but some are also small pyramidal cells and nonpyramidal types. The third reason for proposing the current mechanism is that cholinergic afferents are module-specific; cholinergic axons terminate wholly within individual cortical modules. The cholinergic afferents may be unique in this regard. Finally, the tapering apical dendrites of pyramidal cells are proposed as primary sites for cholinergic mediation of linkages between MAP-2 and microtubules because especially high amounts of MAP-2 are found here. Also, the possibility is raised that muscarinic actions on MAP-2 could modulate microtubular coherence and self-collapse, phenomena that have been suggested to underlie consciousness.

INTRODUCTION

Since the earliest neurochemical investigations, it has been known that acetylcholine release in the cerebral cortex correlates with conscious arousal. Higher levels of acetylcholine are released when we are awake or dreaming than when we are in a light sleep or unconscious in a deep sleep (Celesia & Jasper, 1966; Jouvet, 1975). A causal relationship has been established; acetylcholine induces cortical and conscious arousal. Giving drugs that increase acetylcholine to subjects in deep sleep, for example, causes them to begin to dream (see Hobson, 1990). Still, there is a large gap between identifying a neurotransmitter that enables conscious arousal and explaining

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the process that gives us our sense of self—our intellect—our ability to remember. The latter complex phenomena are also referred to as consciousness, more precisely higher consciousness.

In this present paper, consciousness is defined as mental activity such as percepts, imagery, or abstract concepts (see Baars, 1988, for further description). Higher consciousness is also defined here by its chief characteristics. A dominant feature of higher consciousness is that many features are unified into a gestalt, or whole. Consciousness is largely unified even in split-brain patients; it takes special experimental procedures to reveal the existence of a divided consciousness in these surgically operated individuals (see Zaidel, 1994). Embedded within the unified gestalt principle, conscious experience is presently defined as having three main characteristics: (1) momentary spatial unity, (2) temporal continuity, and (3) a relationship to focused attention (see Greenfield, 1995). It is the way in which cholinergic neurons mediate these features of consciousness that is the topic of this paper.

The model presented here is similar to other models in that it is based on neuron assemblies (e.g., Kinsbourne, 1993) or modules (e.g., McClelland, 1994); however, the emphasis is placed on one particular aspect of cortical circuitry, namely the cholinergic afferents. I will present several arguments why the cholinergic afferent neurons are likely to be the primary guides of conscious activity. My arguments are not incompatible with notions that, especially under certain circumstances, monoaminergic afferents play similar roles to those of the cholinergic afferents and that the intrinsic circuits of the cerebral cortex acting via amino acid neurotransmitter receptors are also critical to consciousness (e.g., see Flohr 1991, 1995). The point here is not to explain the entire neurochemistry of the brain, but rather to decide whether or not we can identify a unified neurotransmitter system that is capable of orchestrating the selection of postsynaptic sites in the cortex to be activated during a conscious moment and how this could be achieved.

One of the first questions we must address is whether cholinergic afferent neurons are metaphorically more a part of the cerebral cortex than separate from it. Although the cell bodies of these cortical afferents lie in the basal forebrain (see Fig. 1), the cholinergic synapses in the cerebral cortex are an integral part of cortical circuitry. Moreover, a large part of the cholinergic neuron—its extensive axonal network—resides in the cerebral cortex. For these reasons, I suggest that these cholinergic neurons be viewed as being more a part of the cerebral cortex than separate from it. This becomes important if we care to say where, if anywhere, we believe consciousness exists in the brain. To simplify the situation, I would view the cholinergic basal forebrain cells as being similar to certain horizontal cells of the cerebral cortex, except that the cholinergic neurons have their cell bodies tightly aggregated outside the cerebral cortex, thereby giving these cholinergic neurons an even greater capacity to integrate activity in the various vertical columns of the cerebral cortex (see Fig. 2, further details are given in the figure legend).

The cholinergic basal forebrain neurons also are in some ways unified with cholinergic cells in the pontomesencephalon. A pathway from the cholinergic pontomesencephalon to the cholinergic basal forebrain that in turn projects to the cerebral cortex (see Fig. 1) replaces the older notion of a nonstop pathway originating in the

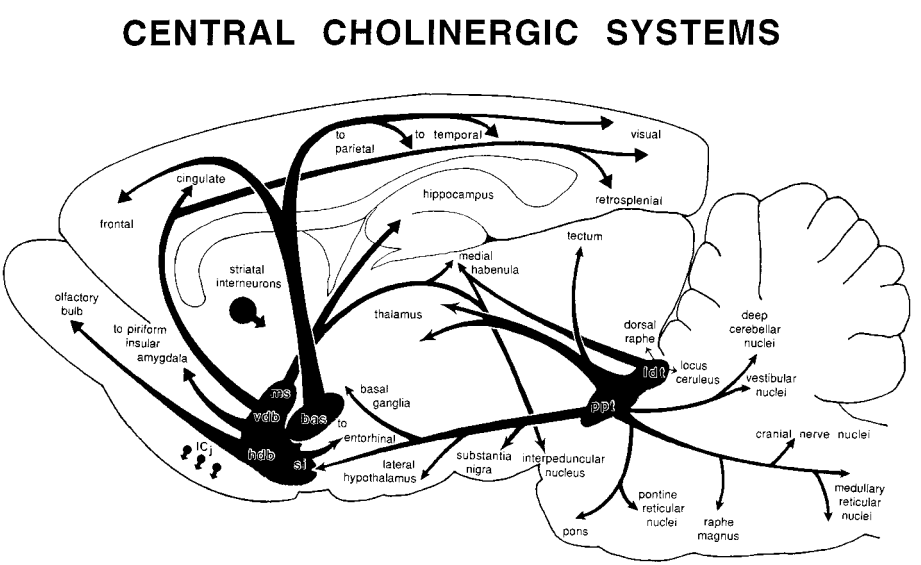

FIG. 1. Cholinergic neurons in the basal forebrain and pontomesencephalon have widespread projections. Cholinergic neurons in the basal forebrain, including those in the medial septal nucleus (ms), vertical diagonal band nucleus (vdb), horizontal diagonal band nucleus (hdb), substantia innominata (si), and nucleus basalis (bas), project to the entire cerebral cortex, hippocampus, and amygdala. Cholinergic neurons in the pontomesencephalon include those in the pedunculopontine nucleus (ppt) and laterodorsal tegmental nucleus (ltd) and have ascending projections to the basal forebrain and thalamus. This figure is reprinted from *Progress in Neurobiology,* **37,** Woolf, N. J., Cholinergic systems in the mammalian brain and spinal cord, p. 482 (1991) with kind permission from Elsevier Science Ltd., The Boulevard, Langford Lane, Kidlington OX5 1GB, UK. The original after which this version is rendered appeared in Woolf, 1983.

cholinergic reticular formation that reaches the cerebral cortex (see Woolf & Butcher, 1986; Woolf, Harrison, & Buchwald, 1990; cf. Shute and Lewis, 1967). Recent studies reexamining early interpretations regarding reticular activation of the cerebral cortex conclude that cholinergic neurons in the pontomesencephalon, along with monoaminergic and neurochemically unspecified neurons, may mediate conscious arousal through their connections with the cholinergic basal forebrain (Jones & Cuello, 1989; Semba, Reiner, McGeer, & Fibiger, 1988; cf. Moruzzi & Magoun, 1949).

Since many neurotransmitters are potentially involved in consciousness, it would be useful to clarify the role played exclusively by cholinergic neurons. A good case in point when cholinergic neurons come close to acting alone may be during dreaming. Cholinergic neurons in the pontomesencephalon appear to be critical to the initiation and maintenance of rapid eye movement (REM) sleep, whereas serotonergic and noradrenergic neurons appear to be inhibited at this time (see Hobson, 1992, for review). Because we usually isolate ourselves from sensory stimuli when we go to sleep, we would expect sensory activation of glutamatergic pathways also to be mini-

mal. Assuming that the neurochemical events observed with REM sleep have anything whatsoever to do with dreams, we might conclude that at least one aspect of consciousness—the ability to form visual or auditory images in the absence of stimuli—is preferentially mediated by cholinergic neurons. If this interpretation is valid, then it clearly demonstrates that cholinergic neurons can determine content. Concerning conscious awareness of realistic stimuli, many arguments can be made for the primary involvement of cholinergic neurons in this instance, as well.

CHOLINERGIC NEURONS AND MOMENTARY SPATIAL UNITY

There is some evidence that conscious experience may correlate with momentary synchronization of cortical activity. Coherent oscillations in the range 30–50 Hz have been found in a number of experimental situations, suggesting a relationship between this kind of activity and perceptual or behavioral decisions. Coherent cortical activity near 40 Hz was originally discovered in the visual cortex and it appeared to be related with the recognition of visual stimuli (Gray & Singer, 1989). Recently, Desmedt and Tomberg (1994) elegantly described transient periods of synchronous activity around 40 Hz in distant cortical sites, namely in the prefrontal and parietal cortices located some 9 cm apart. These authors suggest that this synchrony could be transmitted by corticocortical connections (see Desmedt & Tomberg, 1995). However, there are possible problems with corticocortical connections mediating cases of cortical synchrony, such as mismatches that may occur due to synaptic delays and also that there may be no corticocortical connections between cortical areas where transient synchrony may occur. It has also been suggested that gap junctions may mediate coherent activity. Gap junctions between cortical neurons are common during development (see Kandler & Katz, 1995), and more extensive gap junction networks exist between astrocytes (Konietzko & Muller, 1994). Still, gap junctions may not be present between adult cortical neurons, and even if they occur sparingly, linkages between cortical regions as far apart as 9 cm are hard to explain.

The alternative hypothesis presented here is that the cholinergic afferents mediate cortical synchrony. This hypothesis is attractive for many reasons. First, the hypothesis is plausible. Stimulation of the basal forebrain cholinergic afferents causes cortical neurons to shift from 1–5 Hz phasic activity to tonic firing in the range of 20–40 Hz (Metherate, Cox, & Ashe, 1992), even though the endogenous substrate for these gamma-band oscillations may originate from intrinsic cortical circuitry (see Brett, Krishnan, & Barth, 1996). Second, cholinergic afferents offer a more flexible anatomical substrate than corticocortical connections. Virtually any combination of cortical regions might be co-activated by cholinergic afferents.

Cholinergic basal forebrain cells project to individual cortical modules (Fig. 2). Projection patterns of cholinergic basal forebrain neurons were determined by infusing different fluorescent retrograde tracers into many different cortical areas. In these experiments, double-labeling was rare when tracers were separated by 1–2 mm thereby indicating that although cholinergic basal forebrain neurons provide afferents to the whole cerebral cortex, individual cholinergic neurons innervate modules of cortex measuring approximately 1–2 mm^2 (Bigl, Woolf, & Butcher, 1982; also see Woolf, 1991, for review). Dendrites of cholinergic basal forebrain neurons projecting

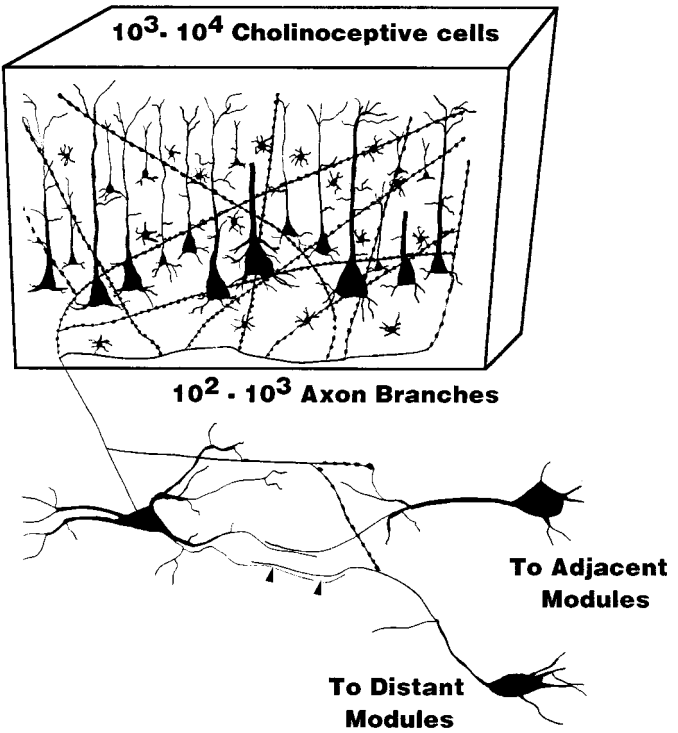

FIG. 2. A schematic representation of the MAP-2-enriched cholinoceptive cells in a module of the cerebral cortex (top part of the figure) and the cholinergic cells that innervate this and other cortical modules (bottom part of the figure). Possible dendritic interactions and traditional synapses are illustrated, which link cholinergic cells with other cholinergic cells projecting to adjacent, as well as to distant, cortical modules. Arrowheads point to possible points of contact between dendrites of neighboring cholinergic cells in the bottom part of the diagram.

to adjacent or to distant cortical modules frequently overlap or bundle together and sparse synaptic interconnections exist (Fig. 2). At closely adherent loci, these dendrites could communicate through gap junctions. It is plausible that phase-locked 40 Hz activity in multiple cortical sites is activated by cholinergic afferents deriving from phase-locked neighboring basal forebrain neurons linked through possible gap junctions that have the ability to couple and uncouple (see Woolf, 1996a, 1996b, for discussions). There is mildly suggestive evidence that a protein matrix may exist enabling gap junctions to transiently link cholinergic cells. An antibody recognizing a sequence from the gap junction protein connexin-32 labels the subsurface cisterns on cholinergic dendrites at sites lying close to cholinergic boutons, presumably deriving from other cholinergic cells (Nagy, Yamamoto, & Jordan, 1993). However, it is not clear what function is served by a connexin-32-like protein at these postsynaptic specializations, and it may play a role in calcium mobilization (Yamamoto, Hertzberg, & Nagy, 1991). In the absence of hypothetical gap junctions linking cholinergic

neurons, sequentially firing cholinergic neurons have another means to induce synchronous activity in distant cortical regions. Cholinergic afferents are exceptionally plastic and capable of restructuring their terminals in the cerebral cortex (see Woolf, 1996b, for review). Through restructuring, cholinergic afferents have the capacity to override the problem of synaptic delay. For example, synapses downstream in the sequential cascade might be altered to effect more rapid postsynaptic responses by moving closer to the postsynaptic cell body. These principles may also apply to monoaminergic afferents, but the monoaminergic cortical afferents are more diffusely organized than cholinergic afferents and it remains to be more fully clarified how the module-specific cholinergic afferents are functionally different from the more diffuse monoaminergic afferents.

When discussing momentary spatial unity, one must define the discrete time interval for a conscious moment, in other words, an indivisible unit of cohesive conscious activity. In some instances, conscious awareness occupies all of our mental effort, while during other times, we are less aware of what we are thinking about or doing. Baars (1988) has distinguished these two events as conscious versus unconscious activity. I would prefer to call what Baars describes as conscious activity ''effortful consciousness'' because these moments seem to take all our attention and mental effort. Alternatively, I would prefer to use the term ''effortless consciousness'' instead of the term ''unconscious'' for mental activities that are less consuming. Unless stipulated otherwise, I am referring to effortful consciousness. This unit may correspond with the time it takes to become aware of a novel or complex stimulus. Libet, Pearl, Morledge, Gleason, Hosobuchi, and Barbaro (1991) suggest that it takes approximately one half a second for continuous thalamocortical activity to produce conscious awareness of a stimulus; stimuli presented for shorter intervals may be detected but this may not be accompanied by a sense of conscious awareness. Other accounts similarly suggest a moment of consciousness lasts several hundred msec. For example, studies of short-term memory show that stimuli presented 200–700 msec after a target stimulus have the best chance of being remembered (Reeves & Sperling, 1986). These results suggest that there is an attention gate that opens for this short time period and then closes. This envelope may correspond to the duration of conscious awareness or the latency to awareness.

Although opinions differ on this point, I would argue that this envelope should be considered as the duration of a conscious moment because information throughout the period contributes to awareness, even if all of it is not remembered equally well. Also, we might argue that at least a readiness for conscious awareness exists continuously, because when we are awake intense stimuli presented at virtually any time will usually reach conscious awareness; there are no absolute blackout periods during normal wakefulness. Nonetheless, it may be impossible to prove whether or not we are continuously conscious. Dennett (1991) has argued that the brain may fill in for gaps in consciousness, giving only the impression of continuity. Jaynes (1976) has further argued that there must be gaps in consciousness due to the time it takes for neurons to fire or communicate through chemical neurotransmission. With all these cautionary notes in mind, I find it simplest to assume consciousness is virtually continuous, and until this point is proven otherwise, I also am assuming that the continuous flow is made up of sequentially linked moments of consciousness.

Activity cycles of cells intrinsic to the cerebral cortex may correspond to these discrete intervals comparable to a conscious moment, but anatomical connections in the cerebral cortex appear to have limited ability to synchronize activity (Eggermont & Smith, 1996). Alternatively, the activity cycles of cortical afferents such as the cholinergic basal forebrain neurons could be the time keepers, thereby imposing synchronous activity within intervals representing the conscious moment. Cholinergic neurons exhibit endogenous activity cycles of about the same time it takes for a stimulus to reach conscious awareness. Isolated cholinergic neurons in basal forebrain slices, for example, have burst cycles lasting 200–600 msec (Khateb, Mühlethaler, Alonso, Serafin, Mainville, & Jones, 1992). The cholinergic neurons in the pontomesencephalon also organize neural activity into intervals of about 500 msec, suggesting they may be another source of this rhythm. The responses of these pontomesencephalic neurons have latencies of 65–500 msec, during which time activity across multiple and diverse sensory channels is integrated (Koyama, Jodo, & Kayama, 1994). Pontomesencephalic cholinergic neurons shunt these integrated responses to the forebrain by way of axons sent to the thalamus and basal forebrain (Woolf & Butcher, 1986). Cholinergic neurons in the pontomesencephalon appear to affect the activity of those in the basal forebrain via the release of acetylcholine (Consolo, Bertorelli, Forloni, & Butcher, 1990) or glutamate (Rasmusson, Clow, & Szerb, 1994).

Clues to what happens during a conscious moment may be garnered from studies on the effects cholinergic afferents have on cortical processing of sensory information. The cholinergic innervation provided by the basal forebrain profoundly enhances the cortical processing of incoming stimuli. This has been shown in auditory, somatosensory, and visual cortex (Donoghue & Carroll, 1987; Metherate & Weinberger, 1990; Sillito & Kemp, 1983). These findings are well known and it is often assumed that this cholinergic modulation merely reflects the ad hoc adjustment of intrinsic cortical function. Closer scrutiny, however, reveals that acetylcholine affects the content of sensory processing. Metherate and Weinberger (1990) probed this issue and determined that acetylcholine specifically alters sensory processing in a context-dependent manner that is determined by previous experience. This result is consistent with the central hypothesis stated in the present paper that cholinergic synapses in the cerebral cortex play a much larger role in the ‘‘intrinsic’’ cortical function than previously thought.

Other clues to what happens during the several hundred msec occupied by a conscious moment may be partly revealed in the P300, an evoked potential with established relationships to consciousness that occurs at approximately 300–500 msec after a novel or oddball stimulus. The P300 wave is not an indicator of mere sensory processing; it complexly reflects information processing, sensory discrimination, and short-term memory (Donchin, 1981). Interestingly, coherent activity near 40 Hz is a component of the P300 cognitive evoked potential (Basar-Eroglu & Basar, 1991). In particular, 40 Hz activity frequently occurs near the end of the 300 msec envelope of the P300 response.

We have done lesion studies in cats and our interpretation of the results was that the positive P300 wave critically depends on cholinergic basal forebrain neurons (Harrison, Buchwald, Kaga, Woolf, & Butcher, 1988). Other investigators have

reached the same conclusion. For example, following damage to the cholinergic basal forebrain, only cholinergic replacement can restore normal evoked response potentials (Ikeda, Egashira, Yamashita, & Okoyama, 1995). Even though other neurotransmitters such as norepinephrine (Pineda, Foote, & Neville, 1989) have been implicated in cognitive evoked potentials, a reasonably strong case is made for cholinergic participation. Judging from all the relationships covered here, cholinergic afferents may go far in determining the time course and content of individual conscious moments.

CHOLINERGIC NEURONS AND THE STREAM OF CONSCIOUSNESS

In one of the earliest written works in the field of psychology, William James (1890) made the following comments about the stream of consciousness:

> These lingerings of old objects, these incomings of new, are the germs of memory and expectation, the retrospective and prospective sense of time. They give that continuity to consciousness without which it could not be called a stream. (pp. 571–572)

In order to keep a stream of consciousness flowing, we might assume that the neurons putatively directing consciousness must be continuously active, even though they may speed up and slow down (e.g., during wakefulness and sleep). Consistent with the present hypothesis, cholinergic neurons may be capable of mediating this flow, because they possess at least two special features relevant to producing the continuous activity deemed necessary for unifying consciousness temporally.

One of these features relates to neurotrophins—molecules that maintain neuronal function and survival. Cholinergic basal forebrain neurons are among a select group of central neurons that are unusually receptive to and dependent on neurotrophins in adulthood (Barde, 1994; Woolf, Gould, & Butcher, 1989). This dependency mandates that cholinergic neurons be continuously active, because their intercellular machinery depends on activity to take up the neurotrophins (see Woolf, 1996a, for discussion). Since incoming stimuli are unreliable sources of activation (especially during sleep), it remains unresolved how basal forebrain neurons stay active during all phases of sleep and wakefulness (see Szymusiak & McGinty, 1989). One possibility is that basal forebrain neurons continuously activate each other through their local interconnections (see Woolf, 1996a). These interconnections between the cholinergic neurons may ensure that neurons not having experienced much recent activity would be activated eventually. Because the previous history of activity would influence future activity, each moment of consciousness produced by such an arrangement would be complexly linked to the next.

Besides having unusual sensitivities to neurotrophins, cholinergic neurons also possess pacemaker qualities that enable them to fire spontaneously. As mentioned earlier, cholinergic basal forebrain neurons are spontaneously and rhythmically active, even when isolated from other neurons (see Khateb et al., 1992). Although cholinergic cells are not the only pacemaker cells in the brain, many neurons do not have intrinsic pacemaker properties. Neurons in the thalamus, for example, lack an intrinsic pacemaker even though they participate in many oscillatory loops (Buzsáki, 1991). The ability of neurons to generate spontaneous activity, in the absence of incoming sensory input, is arguably essential for maintaining temporal continuity of

consciousness. Otherwise, the stream of consciousness would be wholly dependent on incoming stimuli, and there are many examples in which this is not the case (e.g., abstract thinking and dreaming).

Perhaps cholinergic basal forebrain neurons activate the cerebral cortex in a manner analogous to that of cholinergic cells activating the retina. During prenatal development before sensory inputs arrive, spontaneous waves propagate in a mosaic pattern and sequentially activate all parts of the retina; the neurons driving this spontaneous activity appear to be the cholinergic amacrine cells dispersed in a bistratisfied layer next to the ganglion cells (Feller, Wellis, Stellwagen, Werblin, & Shatz, 1996). For the sake of example, we could compare the cholinergic basal forebrain cells to the cholinergic amacrine cells and the cortical pyramidal cells to the retinal ganglion cells. On the basis of this comparison, the cholinergic basal forebrain neurons would transiently activate all parts of the cerebral cortex over time, even in the absence of other driving inputs. Accordingly, one role of the cholinergic basal forebrain cells would be to guide the stream of activity in the cerebral cortex, both in and out of the context of sensory pathway activation.

CHOLINERGIC NEURONS AND AWARENESS OF STIMULI

Even though attention is not the exact equivalent to consciousness, it is generally agreed that a stimulus must be receiving attention to reach conscious awareness. Since sensory information does not always reach conscious awareness, one hypothesis is that activation of the cholinergic systems is a prerequisite. This idea is not new; several investigators have hypothesized that cholinergic basal forebrain neurons mediate selective or focused attention (see Dunnett, Everitt, & Robbins, 1991; Voytko, Olton, Richardson, Gorman, Tobin, & Price, 1994). These investigators define attention operationally, and measure it as a performance level in tasks depending on attention. Deficits in attentional focusing are caused by lesions in the nucleus basalis; however, performance deficits can be overcome if the duration of the stimulus is extended (see Muir, Everitt, & Robbins, 1994). At a first approximation, this result seems quite surprising. Given the module-specific organization of cholinergic afferents, one might expect an all-or-none effect following basal forebrain lesions, depending on whether the cortical modules involved with the task were deafferented. That far fewer cholinergic neurons can still focus attention—but that it takes longer—suggests that cholinergic neurons are doing more than merely fine-tuning intrinsic cortical processing. It argues for the participation of perhaps the whole cholinergic system in each decision of what deserves focused attention. Since many modules of the cerebral cortex are similarly deafferented, it is not surprising that comparative differences in activation by cholinergic afferents are still possible.

I strongly believe that the heart of the consciousness awareness issue lies in this decision of which sensory inputs will receive attention. Sensory inputs themselves are often meaningless unless they are viewed according to a scheme of learned relationships or within a particular context. Thus, in my opinion, it is incorrect to view the attentional role of cholinergic neurons as merely modulatory. By directing attention at specific constellations of circuits in the cerebral cortex, the cholinergic system may well be constructing gestalts from individual sensory inputs relayed by glutamatergic

circuits. After all, awareness of stimuli is a gestalt thought process. We know this because actual sensory inputs are often distorted to fit a particular idea. For example, the Muller-Lyer illusion shows us that two lines of equal length are perceived as having different lengths based on the contextual cues that differentially suggest that line as being part of a larger versus a smaller figure. Gregory (1978) has argued that size constancy—the psychological function of perceiving objects at different distances as being relatively the same size—accounts for the Muller-Lyer illusion. Thus, the percept is based on the relationship between stimulus inputs; the actual inputs are virtually meaningless outside of these relationships. According to this line of reasoning, cholinergic afferents would simultaneously activate constellations of cortical circuits encoding particular sensory inputs and thereby determine the content of conscious awareness during perception; hence, the percept *is* the relationship between stimulus inputs.

Cholinergic neurons may work with other systems in promoting awareness of stimuli or the cholinergic neurons may mediate roles that have been attributed to other neurons. Awareness of stimuli has been attributed to activity in the reticular and the intralaminar nuclei of the thalamus, for example (Bogen, 1995; Crick, 1984; see also Koch, 1995). It is well known that the intralaminar thalamus contains a large number of fibers-of-passage, as does the reticular thalamus; however, that the intralaminar thalamus and the reticular nucleus of the thalamus are major conduits of numerous cholinergic fibers-of-passage has not received sufficient attention. Cholinergic fibers arising from neurons in the pontomesencephalon traverse the intralaminar and reticular thalamic nuclei on route to the basal forebrain (Woolf, Harrison, & Buchwald, 1990). It seems that the regulation of cortical arousal has been mistakenly attributed to the neurons in the intralaminar thalamus, based on the route taken by this cholinergic pathway. Much of the problem lies with faulty premises made in some of the earliest studies on the topic. For example, it was noted early on that stimulation of the intralaminar thalamus increases cortical activity and release of acetylcholine (Jasper & Koyama, 1969). Thus, it was concluded that the neurons in the intralaminar thalamus were responsible for cortical arousal and acetylcholine release. In this same study, however, glutamate release in the cerebral cortex was not affected by stimulation of the intralaminar thalamus (Jasper & Koyama, 1969). Since it is now known that thalamocortical neurons release glutamate in the cerebral cortex (Ottersen, Fischer, & Storm-Mathisen, 1983), it must have been the cholinergic fibers-of-passage en route to the cholinergic basal forebrain that were strongly activated by intralaminar thalamic stimulation resulting in acetylcholine release and cortical activation in that early study by Jasper and Koyama (1969). This means that the role in cortical arousal previously attributed to the intralaminar thalamus may instead be attributable to cholinergic neurons.

Some recent studies further implicate that increased acetylcholine release by basal forebrain neurons into the cerebral cortex plays a role in attention mechanisms. Microdialysis measures *in vivo* show that acetylcholine release is increased in the cerebral cortex when new sensory stimuli receive attention (Inglis & Fibiger, 1995). These increases in release outlast the stimulus duration by many minutes. An even longer lasting enhancement of acetylcholine release can be achieved through the upregulation of the cholinergic synthetic enzyme, choline acetyltransferase. Cholinergic

basal forebrain neurons appear to mediate the selective attention component of associative learning by increasing the mRNA for choline acetyltransferase (Oh, Edwards, & Woolf, 1996). Increased mRNA for choline acetyltransferase may intensify acetylcholine release in select cortical modules for several days. Intensified release of acetylcholine that persists for minutes to days is hypothesized to induce structural change and memory encoding, thereby forming a permanent record of selectively focused attention (Woolf, 1996b). These structural modifications hypothetically rearrange release sites of acetylcholine and alter the cytoskeletal matrix at postsynaptic sites on cholinoceptive cells, thereby converting extended periods of enhanced acetylcholine release into brief (msec) periods of acetylcholine release capable of mediating conscious awareness involved in recognition and retrieval processes (see Woolf, 1996a, for further discussion). Since structural changes at postsynaptic sites on cholinoceptive cells appear to involve the degradation of microtubule-associated protein-2 (MAP-2), linkages between MAP-2 and the cytoskeletal matrix may play a role when those modified muscarinic cholinergic synapses are reactivated during conscious moments of recognition and retrieval.

POTENTIAL CHOLINERGIC ACTIONS ON MICROTUBULE-ASSOCIATED PROTEIN-2

The specific prediction of the present model is that cholinergic neurons direct consciousness through signal transduction steps that affect MAP-2 in cortical cells. MAP-2 is a structural protein found in dendrites and one of its dynamic functions is to modulate the stability of microtubules through direct linkages with cytoskeletal elements (see Johnson & Jope, 1992, for review). Microtubule-associated proteins, including MAP-2, link microtubules, microfilaments, neurofilaments and receptors embedded in the membrane (Maccioni & Cambiazo, 1995). MAP-2 may also participate in neuronal signaling. Quinlan and Halpain (1996) have recently shown that MAP-2 is rapidly dephosphorylated by NMDA receptor activation—possibly qualifying MAP-2 as a signal transduction molecule. This vastly expands potential roles for MAP-2 in neural functioning. While there is currently no direct evidence for muscarinic receptor activation of MAP-2 phosphorylation, the second messengers in the muscarinic receptor cascade do rapidly phosphorylate MAP-2. Moreover, the anatomical evidence points to a special relationship between muscarinic receptors and MAP-2. In addition to independent muscarinic effects on MAP-2, muscarinic actions may also enhance NMDA actions on MAP-2. A critical role for NMDA receptors in consciousness has recently been hypothesized by Flohr (1991, 1995).

In their recent quantum theory model, Hameroff and Penrose equate consciousness with a momentary self-collapse in the coherence of microtubules; MAP-2 or other microtubule-associated proteins are suggested to orchestrate these events (Hameroff & Penrose, 1995; Penrose, 1994). Although we still do not know for certain if microtubular coherence is related to consciousness, cholinoceptive cortical neurons would be expected to play a significant role in this proposed process because they contain abundant amounts of MAP-2. Even though all neurons contain microtubules and microtubule-associated proteins, specifically those cells in the cerebral cortex that react with antibodies to muscarinic receptor have appreciably high levels of MAP-2

in the cell body and the large apical dendrites (Woolf, 1993). Moreover, these concentrated deposits of MAP-2 within cholinoceptive cells seem to play a role in cognition. With classical conditioning to tone, the cholinoceptive cells within discrete modules of auditory cortex show signs of MAP-2 degradation (Woolf, Young, Johnson, & Fanselow, 1994). Similar changes appear in CA1 and CA2 subsectors of the hippocampus with contextual learning (Woolf, Zinnerman, & Johnson, 1996). Ways in which cholinergic afferents may critically modulate dendritic restructuring through effects on MAP-2 have been recently summarized (see Woolf, 1996b). Briefly, changes in MAP-2 phosphorylation state and its degradation could be triggered by muscarinic receptor stimulation of NMDA actions, Ca^{+2} mobilization, and signal transduction molecules, including several protein kinases. Once MAP-2 linkages with microtubules are rearranged by the learning process, these new linkages may play a role in conscious awareness. This idea is somewhat compatible with the suggestion of Hameroff and Penrose (1995) that microtubule-associated proteins ''tune'' microtubular coherence at their attachment sites.

Microtubular coherence occurs when water molecules in tubulin dimers collectively enter an excited state (see Jibu, Hagan, Hameroff, Pribram, & Yasue, 1994). One of the reasons cytoskeletal microtubules are good candidates for quantum coherence is that their paracrystalline structure, cylindrical shape, and parallel alignment promote long-range cooperativity and order (Hameroff, 1994). The hollowness of the microtubular core may also be important for the ordering of water molecules and for the enabling of a process called ''superradiance,'' in which energized particles are able to penetrate the microtubule like a laser because of the induction of another process called ''self-transparency'' (see Jibu et al., 1994). Hameroff and Penrose (1995) stipulate the coherence of approximately 10^9 tubulin molecules in the mediation of a moment of consciousness; this is based on a 500 msec time to collapse. This much tubulin is enough to fill approximately 10^2–10^4 neurons, depending on the percentage of tubulin involved per neuron (appreciably more tubulin molecules would be involved with shorter coherence times to collapse). Multiple minicolumns must be activated to represent even a simple gestalt, since each minicolumn represents only one very specific feature—such as a line segment of a particular orientation. Minicolumns throughout the cerebral cortex contain some 100–200 neurons (Mountcastle, 1978; Peters & Yilmaz, 1993); therefore, the predicted number of neurons exhibiting microtubular coherence leading to self-collapse possibly comprises too few minicolumns to form meaningful gestalts. This limit is easily overcome if only select postsynaptic sites on select neurons participate. Microtubules and microtubule-associated proteins are found in all neurons; however, MAP-2 enriched cholinoceptive neurons account for only 15% of neurons in the cerebral cortex (Woolf, 1993). Many of the MAP-2 enriched cholinoceptive neurons are the large pyramidal cells; however, some are smaller pyramidal and non-pyramidal cells (Fig. 2). The point here is that approximately the same number of MAP-2 enriched cholinoceptive neurons occupy a 1–2 mm^2 module of cortex (10^3–10^4) as the number of neurons predicted by Hameroff and Penrose to be involved in microtubular coherence and self-collapse (10^2–10^4; based on the involvement of 1–10% of the tubulin in each neuron and a 500 msec time to self-collapse). Moreover, Jibu and colleagues (1994) have suggested that quantum coherence is capable of coupling microtubules spatially dis-

tributed over several hundred microns. Finally, it seems that a module of cortex contains the exact complement of minicolumns encoding all the specific features of the same modality (see Mountcastle, 1978) and would be a highly appropriate unit of cortex within which to activate gestalts.

The central hypothesis of this paper is that cholinergic neurons co-activate certain postsynaptic sites in a select number of modules dispersed throughout the cerebral cortex. There is currently no basis from which to make an estimate of how many modules might simultaneously participate in a conscious moment and it is entirely possible that the number of participating modules varies greatly. During effortful consciousness, we might expect fewer modules to be involved and the time interval of a conscious moment to be on the long side (near 500 msec). During effortless consciousness, we might expect larger numbers of modules to be involved and the time interval to be shortened (near 100 msec). The basic mechanism could be the same in effortful and effortless consciousness; however, the timing of events would be different. It is conceivable that following repeated usage what was once effortful becomes effortless, presumably due to changes in the underlying structure facilitating interactions between more modules. This prediction is borne out by the fact that the more microtubules involved in quantum coherence, the shorter the time to self-collapse (Hameroff & Penrose, 1995).

These speculations may seem plausible, but is there any evidence that muscarinic receptor activation can induce coherent activity of any kind? It appears that muscarinic acetylcholine receptors present in membranes of non-neuronal cells do evoke coherent Ca^{2+} waves (Lechleiter, Girard, Peralta, & Clapham, 1991), which also may be involved in hardwiring the structure of cytoskeletal proteins in neurons (see Jibu et al., 1994). For muscarinic receptor activation to induce microtubular coherence, however, a rapid process such as phosphorylation is needed. Recently, muscarinic actions have been shown to dephosphorylate the microtubule-associated protein, tau (Sadot, Gurwitz, Barg, Behar, Ginzburg, & Fisher, 1996). Although it has not been shown directly, phosphorylation of MAP-2 is likely to occur following muscarinic receptor and G-protein activation. MAP-2 is phosphorylated by protein kinases: PKC, PKA, Ca^{+2}/calmodulin kinase, and the serine-threonine MAP kinase (see Johnson & Jope, 1992), and muscarinic receptors activate these protein kinases (Cantrell, Ma, Scheuer, & Catterall, 1996; Lee & Fraser, 1993; Müller, Petrozzino, Griffith, Danho, & Connor, 1992; Offermanns, Bombien, & Shultz, 1993; Pedarzani & Storm, 1996). Cholinergic muscarinic receptor and G-protein activation trigger these protein kinases which would be expected to decrease MAP-2 co-assembly with microtubules, because phosphorylation decreases the availability of MAP-2 to bind to microtubules (Ainsztein & Purich, 1994; Diez-Guerra & Avila, 1995; Hoshi, Ohta, Gotoh, Mori, Murofushi, Sakai, & Nishida, 1992; Stofko-Hahn, Carr, & Scott, 1992) and the co-assembly of MAP-2 with microtubules is regulated by the availability of MAP-2 (Pryer, Walker, Skeen, Bourns, Soboeiro, & Salmon, 1992; Yamauchi, Flynn, Marsh, & Purich, 1993). Insofar as neurotransmitters and their allied signal transduction molecules regulate the availability of MAP-2 through phosphorylative effects, these neurotransmitters might be expected to affect microtubular coherence leading to self-collapse.

MAP-2 binding sites are evenly distributed along the length of the microtubule

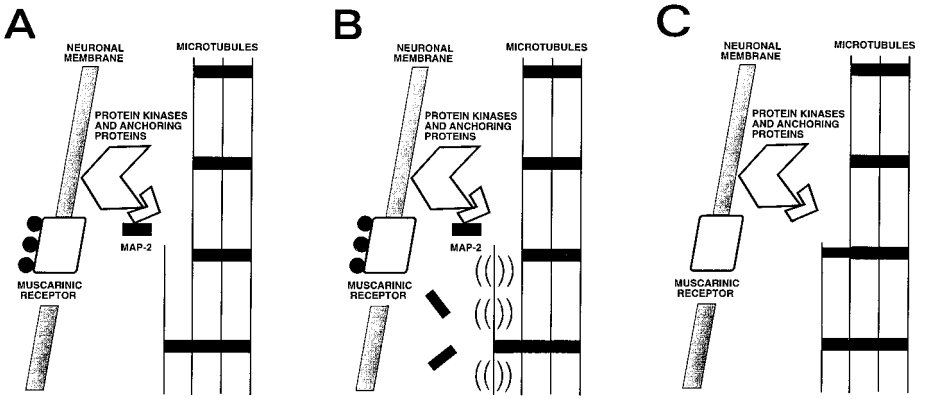

FIG. 3. A hypothetical sequence of events linking muscarinic receptor activation with MAP-2-mediated microtubular coherence and self-collapse. (A) Acetylcholine molecules (black dots) bind to the muscarinic receptor activating the anchored protein kinases that will phosphorylate MAP-2, thereby making MAP-2 unavailable for binding with local microtubules. (B) During the next several hundred msec, phosphorylation of excess MAP-2 prevents it from binding with local microtubules and thereby facilitates microtubular coherence (illustrated as curved lines). (C) When the muscarinic action ends, MAP-2 phosphorylation ceases leaving MAP-2 free to bind microtubules and possibly initiate self-collapse.

(Murphy & Borisy, 1975); however, MAP-2 co-assembly with tubulin occurs prominently at the dynamically elongating and shortening ends of microtubules (see Cassimeris, Pryer, & Salmon, 1988). Even though decreasing the amount of MAP-2 can also disrupt the existing stable arrays of microtubules (Sharma, Kress, & Shafit-Zagarado, 1994), under normal circumstances the stable arrays of microtubules should be relatively resilient to neurotransmitter-mediated modifications. The microtubular ends are more dynamic and many of these ends are associated with the plasma membrane (see Sasaki, Stevens, & Bodick, 1983, for review). There seems to be a high concentration of MAP-2 near the plasma membrane in long tapering dendrites such as the apical dendrites of large pyramidal cells implicating this as a primary site of modification (see Fig. 3).

The events illustrated in Fig. 3 are depicted as occurring in a localized domain surrounding the muscarinic synapse. Protein kinases are anchored by specific proteins. One anchoring protein regulatory subunit, called RIIβ, binds to MAP-2 (Keryer, Cavadore, Erlichman, & Bornens, 1993). The regulatory subunit RIIβ is highly concentrated in mammalian cerebral cortex (Ventra, Porcellini, Feliciello, Gallo, Paolillo, Mele, Avvedimento, & Schettini, 1996), indicating that it is located in the right place to function as proposed in the present model. Muscarinic receptors and the γ subunit of PKC (and possibly the serine-threonine MAP kinase to some extent) are colocalized in the same cortical pyramidal cells that are enriched with MAP-2 (Van der Zee, Douma, Bohus, & Luiten, 1994; Woolf, 1996a).

Presumably, events depicted in Fig. 3 occur simultaneously at multiple postsynaptic sites in multiple cholinoceptive neurons. All of these postsynaptic sites need not

be traditional synapses. Acetylcholine is thought to be released diffusely from varicosities along the axon, and the majority of varicosities do not make synaptic contact (Umbriaco, Watkins, Descarries, Cozzari, & Hartman, 1994). Acetylcholine is presumably released from different sites throughout the module at approximately the same time; this would be especially true for varicosities along a single branch of the cholinergic axon. Cholinergic afferent fibers in the cerebral cortex collateralize extensively into branches; the exact number of collateral branches is not known. Estimates based on fiber counts (see Farris, Butcher, Oh, & Woolf, 1995) suggest that each cholinergic fiber branches into roughly 10^2–10^3 axonal arbors. Each module of cortex is innervated by approximately 10^6 sites of acetylcholine release (based on data in Oh, Butcher, & Woolf, 1991). Theoretically, the positioning of acetylcholine release sites and the geometry of MAP-2 and microtubules in the postsynaptic site would be determined by previous learning experience (see Woolf 1996a, 1996b).

The proposed events begin with cholinergic muscarinic receptor stimulation of signal transduction molecules that simultaneously induce postsynaptic potentials and MAP-2 phosphorylation (Fig. 3A). In cortical pyramidal cells, excitatory synaptic responses to muscarinic receptor activation are slow, with latencies around 250 msec (McCormick & Prince, 1986). During this latency period (Fig. 3B), MAP-2 phosphorylation is predicted to block dynamic linkages between MAP-2 and local microtubules, thereby promoting and prolonging an event such as microtubular coherence. This scenario seems plausible; however, it remains to be empirically determined if phosphorylative events could occur in the appropriate time frame to mediate conscious activity as currently proposed.

Even though only select postsynaptic sites are envisaged as being activated in the current proposal, each postsynaptic site is affiliated with a large number of tubulin molecules because affiliated microtubules collectively extend through the dendrite and into the cell soma through bridges made by microtubule-associated proteins connecting to other microtubules. According to the present model, simultaneous activation or what is sometimes called ‘‘cortical binding’’ would theoretically occur between near or distant postsynaptic sites affiliated with microtubules that share the same lengths and spacing between links with MAP-2 and other microtubule-associated proteins as determined by learning-related restructuring. This proposal is consistent with the fact that the precise timing of an event such as microtubular coherence will depend on the geometry of the cytoskeletal matrix (e.g., the spacing between MAP-2 linkages with the microtubules). While there may be countless patterns in which MAP-2 could bind microtubules of various lengths, whether there are enough diverse structural possibilities to enable the many instances of selective ‘‘cortical binding’’ is a question that might be empirically derived. Although there is an average periodicity for MAP-2 linkages with microtubules, a good deal a variability is evident when direct measurements are made; one explanation is that various domains of the microtubule are composed of different tubulin isotypes (see Kim, Jensen, & Rebhun, 1986). Another critical experiment would be to see if synchronous cortical activity is correlated with similar cytoskeletal structure at key postsynaptic sites. This experiment might be difficult to carry out but perhaps not impossible given a few necessary technical advances.

Muscarinic responses, bounded by the geometry of their postsynaptic sites, might

also be modulated by current microtubular events. This seems likely as it is known that microtubules modulate surface receptors (Maccioni & Cambiazo, 1995). At the end of the muscarinic action (Fig. 3C), decreased phosphorylation of MAP-2 may lead to the assembly of MAP-2 with local microtubules and also to the possible self-collapse of microtubular coherence. It is not clear, however, if MAP-2 assembly with microtubules can occur fast enough to operate as proposed here. From what is known about the time course of microtubule assembly with MAP-2 *in vitro* (see Ainsztein & Purich, 1994), rapid assembly seems possible. To realistically test this hypothetical scheme, one would need an *in vivo* measurement of MAP-2 assembly with microtubules on a small scale. The assembly of a few molecules in a small confined space would presumably take less time than the assembly of a large number of molecules in a larger space; however, this would have to be tested directly due to the unforeseen influences of the local environment. Alternatively, it may be the self-collapse process that promotes cessation of the muscarinic response.

Could self-collapse of microtubular coherence, the completion of muscarinic receptor activation, or both of these two events represent the physical basis of the conscious moment? I would argue that neither is the physical basis of the conscious moment, but that instead these short-lived events may be essential for linking one conscious moment to the next. One might expect that whenever the stream of consciousness is disrupted (e.g., when a person is distracted) that self-collapse of microtubular coherence never occurs because the appropriate set of cholinergic afferents never attains sufficient activation. Accordingly, thermal noise might be expected to disrupt the coherence of microtubules in insufficiently activated circuits and those conscious moments would end in the absence of an abrupt process such as self-collapse. Thus, it is not necessary to stipulate that a process such as self-collapse occurs in order for there to be a conscious moment; however, conscious moments ending without such may be qualitatively different (i.e., fuzzier) and linking to the next conscious moment may be slow and unpredictable.

If the events described here as linking the end of one conscious moment to the next are not the physical substrates of consciousness, what is? I would argue that perhaps it is the coherent state of microtubules affiliated with select postsynaptic sites within select cortical modules orchestrated by the cholinergic afferents that comes closest to representing the physical basis of consciousness. Since each set of activated postsynaptic sites would have its own ‘‘signature’’ set of microtubular lines, this proposal may be able to account for the uniqueness of every conscious moment. The ‘‘conscious moment’’ described here seemingly corresponds to the ‘‘preconscious’’ interval in the Hameroff and Penrose (1995) model. My differing view on this point in no way detracts from the potential significance of the proposed self-collapse mechanism. The transition from one moment of conscious to the next may, by far, be the more complex problem to solve. Here again, however, some answers may be found in a central neurotransmitter system, like the cholinergic system.

CONCLUSIONS

Special properties of cholinergic neurons in the basal forebrain and the pontomesencephalon were presented in this paper, and I have argued that these properties may

enable cholinergic neurons to direct consciousness. The way the present ideas differ significantly from current thinking is the degree to which cholinergic afferent neurons are considered to play a role in ''intrinsic'' cortical functioning. The long-standing view has been that cholinergic afferents merely adjust higher functions performed by the cerebral cortex. For example, McCormick (1992) has argued that executative cortical processing is mediated by the faster-acting neurotransmitter glutamate; accordingly, the slower-acting cholinergic postsynaptic sites highlight that processing. I argue here that muscarinic receptor activation is necessarily slow, not because it plays a secondary role but because it takes a fair amount of time for a systemwide search for similarly ''tuned'' postsynaptic sites.

Hasselmo and his associates (Hasselmo, 1995; Hasselmo & Bower, 1993; Hasselmo & Schnell, 1994) suggest that cholinergic neurons compute decisions regarding how the cortex will operate. They have developed a model in which the cholinergic modulation of the cerebral cortex and hippocampus acts as a switch that changes cortical processing from being influenced by cortical input fibers to being influenced by intracortical fibers, thereby changing cortical function from a learning mode to a recall mode. The Hasselmo model may be partly compatible with the model described here, although it does not go quite so far as to suggest that cholinergic afferents determine the length of the conscious moment and its contents. Both models do, however, emphasize the role of cholinergic neurons in cortical processing.

Along with any heuristic value provided by the present model, it also may have potential for explaining some perplexing cognitive abnormalities. In idiot savant syndrome, for example, individuals simultaneously possess an exceptional talent (e.g., a photographic memory or musical talent) along with an overriding compromise in intellectual ability (see Treffert, 1988, for review). From the current model, it might be predicted that the cholinergic afferents in the cerebral cortex are abnormal in savants. For example, cholinergic fibers might extend beyond the normal boundaries of the cortical module. Thus, the stimuli processed by those abnormally innervated modules would involve more cholinoceptive cells than in a normal brain. This would result in some conscious moments containing more information than normal; however, other conscious moments would be abnormally impoverished. Adding information from outside modules might also be impaired. Thus, savants would have exceptional specialized abilities, but there would also be an overriding mental handicap.

Another syndrome associated with mental retardation is Down's syndrome. Cognitive processing in Down's syndrome may be impaired due to abnormalities in the microtubule-associated proteins, which might affect cholinergic transmission. There is evidence that at least one microtubule-associated protein is more rapidly synthesized and degraded in Down's syndrome brain than in controls (Whatley, Hall, Davison, & Lim, 1984). This defect may affect binding to microtubules and impair responses to muscarinic receptor activation. Consistent with this prediction, the latency of the P300 (which may be mediated by cholinergic afferents) is increased in Down's syndrome (Diaz & Zuron, 1995).

There may also be a correlation between cognitive impairment and MAP-2 function in Alzheimer's disease. The relationship between the two has not been fully revealed, even though such a relationship is suggested. MAP-2 often becomes associ-

ated with the neurofibrillary tangles that accumulate in hippocampal and cortical pyramidal cells of Alzheimer's disease brains, as well as in Down's syndrome patients who prematurely develop a similar profile (Murphy, Eng, Ellis, Perry, Meissner, & Tinklenberg, 1990). Recently, it has been shown that segments of MAP-2 may form neurofibrillary tangles, or alternatively, that abnormally phosphorylated tau sequesters MAP-2 into the neurofibrillary tangles (DeTure, Zhang, Bubb, & Purich, 1996 cf. Alonso, Grundke-Iqbal, Barra, & Iqbal 1997).

In summary, I have proposed that acetylcholine may direct consciousness through a cascade of effects leading to a momentary phosphorylation of MAP-2 that interrupts the binding of MAP-2 to microtubules and promotes a process such as microtubular coherence. The tapering apical dendrite of the pyramidal cell was identified as a probable site for these events. The present model is novel in that it melds cognitive, neurochemical, neurostructure, and possibly quantum physics into a cohesive and testable hypothesis. One obvious test of the sequence proposed here would be to see if muscarinic receptor activation does lead to the phosphorylation of MAP-2 as is expected from what is known about the signal transduction molecules involved.

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