Cholinergic Modulation, Visual Function and Alzheimer's Dementia

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Electrophysiological evidence at a cellular level and *in vivo* macroelectrode recordings converge in indicating a degree of specificity of acetylcholine action in vision. Acetylcholine (ACh) function is also thought to play a significant role in memory, learning and other cognitive processes. In this respect, ACh action is suggested to serve in both sensory and cognitive processes. The pharmacological blocking of brain muscarinic transmission has been proposed as a model of geriatric memory impairment and Alzheimer's dementia. Visual electrophysiological testing is deemed of diagnostic specificity for this disease. ACh brain neurotransmission, however, mostly contributes to the modulation of nonspecific aspects of cognition, such as arousal or attention. Alzheimer's dementia results from complex neuron alterations [which also affect muscarinic receptors among other (sub)cellular structures] rather than simply reflecting ACh impoverishment. A substantial loss of retinal ganglion cells is documented in patients with Alzheimer's disease and is consistent with electrophysiological observations. However, it is unclear to what extent the dysfunction of the visual system observable in Alzheimer's dementia is qualitatively different from that occurring spontaneously during aging. The dissimilarities between the effect of acute muscarinic blocking (e.g. by scopolamine) and dementia outnumber the similarities. Accordingly, the conventional ACh agonist–antagonist model of dementia now appears questionable, and replacement treatment with compounds enhancing ACh function proved disappointing. It is suggested that (nonspecific) ACh action becomes function-specific, as determined by the architecture of local brain circuits in which it is involved. © 1997 Elsevier Science Ltd

Acetylcholine   Cholinergic neurotransmission   Electrophysiology of vision   Retinal function
Lateral geniculate nucleus   Visual cortex   Alzheimer's disease   Aging   Models of dementia

INTRODUCTION

Cholinergic cortical neurons and subcortical pathways projecting to the cortex are thought to mediate in the transfer of information in parallel and serial brain networks (Mesulam, 1995). In contrast with discrete projections from thalamic nuclei to corresponding cortical targets, relatively small cholinergic subcortical systems project to large portions of the cortex and modulate brain activity in ways that are—to an extent—nonspecific with respect to neuronal function. A degree of specificity of acetylcholine (ACh) action is, however, implicated in visual information processing and is also suggested for higher functions, notably memory, learning

and other cognitive processes (Kirby *et al.*, 1986; Sato *et al.*, 1987a,b; Steriade & Biesold, 1990; Fibiger, 1991; Sarter & Bruno, 1994; Sannita, 1995; Mesulam, 1995). A substantial decline in cholinergic markers is the preponderant feature in Alzheimer's disease (a primary degenerative illness accounting for about 70% of cases of dementia; DAT) (Geldmacher & Whitehouse, 1996), and in animal "models" of DAT created by lesioning the basal forebrain structures (Willner, 1991). Accordingly, the pharmacological blocking of brain muscarinic neurotransmission (e.g. by ACh-antagonist scopolamine) has been proposed as a suitable experimental model of geriatric memory impairment and, at large, of DAT and has been extensively used to test putative cholinergic drugs. Conspicuously, the circularity of this approach—using *in vivo* brain as an assay to test cholinergic drugs in the absence of detailed knowledge of sites and mechanisms of ACh action—has been rarely questioned (Drachmann & Leavitt, 1974; Bartus *et al.*, 1982; Kopelman & Corn, 1988; Ridley *et al.*, 1991; Christensen *et al.*, 1992; Muir *et al.*, 1993). Cholinergic agonists and antagonists have also been used as test conditions in the investigation of the role of ACh in visual information processing. The electrophysiology of the visual system

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has been deemed of relevance in the diagnosis of DAT, on the grounds of the suggested ACh-specificity of components of cortical visual evoked responses (Wright et al., 1987; Daniels et al., 1994).

ACH FUNCTION AND VISION

Cholinergic neurons and postsynaptic receptors have been identified in several instances in the retina, lateral geniculate nucleus (LGN) and visual cortices of animals and man and appear to be arranged in subsystems, with roles encompassing a variety of functions (Neal, 1983; Kirby et al., 1986; Schliebs et al., 1989; Pasik et al., 1990; Kageyama et al., 1990; Frey et al., 1992, among many others). There is evidence of early development of the brain ACh systems, which depends on experience and sensory input ACh systems may be interfered with by substantial visual deprivation and the role of ACh in the regulation of cortical plasticity is also known (Dinopoulos et al., 1989; Walch et al., 1989; Kageyama et al., 1990; Schlumpf et al., 1991; Kumar & Schliebs, 1992; Rossner et al., 1993; Gu & Singer, 1993; Liu et al., 1994).

Detailed accounts of ACh action in the retina have been given by Masland & Tauchi (1986); Schmidt et al. (1987), and Jurklies et al. (1996). There are known complex intermodulations among different classes of retinal cells, but there are also numerous discrepancies reported by different studies, that may possibly be due to methodological dissimilarities. Recordings from horizontal cells suggest the absence of cholinergic action in the outer retina (Niemeyer et al., 1981), whereas both muscarinic and nicotinic receptors have been identified in the inner retina of several mammals, including man (Puro, 1985; Pourcho, 1979; Hutchins & Hollyfield, 1987). Two main populations of cholinergic amacrine cells project to the inner plexiform layer from the inner nuclear layer and ganglion cell layer, respectively (Famiglietti, 1983; Pourcho & Osman, 1986). This stratification may serve differential purposes. However, Schmidt et al. (1987) observed that ACh increases (and scopolamine decreases) the firing rate of both ON- and OFF-center ganglion cells irrespective of stimulus condition and with comparable effects on maintained discharge and light-induced activity during center, surround and whole-field stimulation. The ACh modulation on different types of ganglion cell proved unexpectedly concentration-related, which suggests differential sensitivity, and is not as stereotyped as the report by Schmidt et al. (1987) may suggest. In fact, Schmidt et al. (1987) also described distinct effects of the nicotinic antagonist dihydro-β-erythroidine on ON-center and OFF-center cells, and different effects of ACh on ON-center and OFF-center cells (as well as on sustained or transient cells) were described by others. Ikeda & Sheardown (1982) reported an ACh-induced increase of the light-evoked activity of Y cells but not of X cells; ACh-mediated inhibitory action on ON-center ganglion cells and excitatory effects on OFF-center cells have been also observed (Straschill & Perwein, 1973). Physostigmine enhances the ACh excitatory effect in the cat retina,

with a prevalent action on center-dominated responses (Schmidt et al., 1987), and increases both the spontaneous activity and response to stimulation of rabbit ganglion cells, with changes in receptive field properties that depend, in part, on the type of cells (Ariel & Daw, 1982).

ACh-modulated components of the electroretinogram (ERG) and optic nerve response (ONR) were identified in the isolated, arterially perfused cat eye (Jurklies et al., 1996). Notably, ACh and ACh-agonists induce a long-lasting decrease of the rod- and cone-driven ONR and enhance the b-wave (particularly of the cone-driven response), whereas scopolamine decreases it. An early, transient increase of ONR was observed after high doses of ACh-agonists in the cone-driven response, as well as after scopolamine in the rod-driven response. The time dynamics of these effects differed. The nicotinic antagonist mecamylamine showed a biphasic effect on the ERG b-wave, depending on time after administration (rod-driven b-wave) or dose (cone-driven b-wave), and had opposite effects on rod- and cone-driven ONR (Jurklies et al., 1996). Based on this evidence, the complexity of ACh retinal modulation suggests differential action, related to properties of cells and neuronal circuitry, and the existence of ACh-selective components. Further heterogeneity also may result from selective interaction of muscarinic agents with m1 and m2 binding sites (Watson et al., 1986) or from feedback mechanisms also involving other neurotransmitters (Neal & Cunningham, 1994). Additional investigation in these areas is required.

In the visual cortex (as well as in hippocampus), ACh is a potent and long-lasting excitatory agent (McCormick, 1989) modulating the level and temporal patterns of neuronal activation through a direct, postsynaptic effect on pyramidal cells. It reduces three distinct potassium currents (muscarine-sensitive I_M; I_{AHP}; and $I_{K,l}$), the increase of which inhibits the discharge rate of pyramidal neurons. Although muscarinic function is prominent (Spehlmann, 1963), nicotinic and muscarinic receptor subsystems are partly complementary, in that they yield an early excitation of short duration and a later, long-lasting excitation, respectively (McCormick, 1989, 1990; McCormick & Prince, 1987). Microionophoretic application of ACh in the cat striate cortex increases the firing rate in response to receptive field stimulation of the majority of ACh-sensitive cells and exerts a fast, transient inhibitory effect of the remaining cells (Sato et al., 1987a). Muscarinic, but not nicotinic antagonists suppress the facilitatory effect of ACh while enhancing the response of ACh-inhibited cells. The facilitating effect is also suppressed after unilateral lesion of cholinergic nucleus basalis magnocellularis, while ACh counterbalances this effect of lesion (Sillito & Kemp, 1983; Sato et al., 1987a,b). The inhibitory effect occurs via ACh-induced activation of GABAergic interneurons (notably GABA$_A$-receptors) (Müller & Singer, 1989; McCormick, 1989), consistent with the ACh–GABA interaction, reciprocal "tuning" and complementary roles that appear

to serve as a widespread mechanism of regulation in the CNS (Sillito, 1975; McCormick & Prince, 1986; Sarter & Bruno, 1994). Evidence from studies on retinal amacrine cells suggests that this interaction depends on neuronal loops and feedback mechanisms rather than on pre- or postsynaptic inhibitory muscarinic receptors (Cunningham et al., 1983). It is still unclear whether such mechanisms are operative in the cortex as well. Besides interacting with GABAergic neurons, ACh also modulates glycine- and glutamate-dependent NMDA currents (Ben-Ari et al., 1992).

Microionophoretic ACh administration increases the spontaneous firing of ACh-inhibited cells (Müller & Singer, 1989), whereas the spontaneous firing of ACh-facilitated cells is virtually unaffected and remains very low (Sato et al., 1987a). In functional terms, the result of ACh application is the improvement of the "signal-to-background ratio" for ACh-activated cells.* This effect appears congruent with the reduction of interference from synapsing collaterals that is caused by presynaptic ACh action in CA1–CA3 regions of hippocampus (McCormick, 1989; Hasselmo & Bower, 1993). Evidence from studies on the somatosensory cortex suggests that ACh enhances responsiveness by lowering the threshold to stimulation and possibly by increasing the receptive field size (Lamour et al., 1988). Receptive field effects of ACh on visual cortical cells have also been postulated. However, a selective cortical effect of ACh on preferred and non-preferred stimulus directions has been observed in some studies (e.g. Sillito & Kemp, 1983), but denied in others (e.g. Sato et al., 1987a,b; Müller & Singer, 1989).

Subcortical ACh-mediated subsystems regulate the level and coordinated temporal patterns of cortical activation through diffuse projections from the basal forebrain or via thalamocortical loops (Kayama et al., 1986; Robbins et al., 1989; McCormick, 1989; Mesulam, 1995). In the thalamus, ACh has either an excitatory or inhibitory effect depending on the type and the location of the postsynaptic cell; it serves as a "gate" system in the transfer of sensory information to the cortex by adjusting the functional state of thalamic nuclei. Both short-lasting nicotinic and long-lasting muscarinic excitatory effects on the relay neurons of dorsal LGN (mediated by the increase in cation conductance and decrease in K conductance, respectively) have been described (McCormick & Prince, 1987; Curro-Dossi et al., 1991); the effects of ACh on GABAergic local-circuit thalamic interneurons are qualitatively opposite to those on relay neurons (McCormick & Pape, 1988). Local application of ACh or stimulation of brainstem cholinergic neurons both result in increased responsiveness of principal

neurons in the LGN that project to the visual cortex (Sillito & Kemp, 1983). Nonretinal inputs to the LGN from either the ascending cholinergic pathway or the descending pathway from layer VI of the visual cortex affect membrane properties and regulate retinogeniculate signal transmission (Guido & Lu, 1995). No direct cholinergic projection to the visual cortex from the mesencephalic reticular formation has been identified, and this structure is thought to transiently facilitate visual cortex excitability indirectly, through the cholinergic system of basal forebrain (Müller et al., 1993). Detectable levels of glutamate immunoreactivity were identified in a substantial portion of cortical synaptic targets for cholinergic projecting terminals, and there is evidence of intermodulation between ACh and glutamate release at postsynaptic sites (Aoki & Kabak, 1992). Activity in cholinergic (as well as in adrenergic and glutamatergic) pathways, ACh–GABA interaction, changes in thalamic firing patterns or mode, and significant shifts in arousal concur in controlling sensory input to the cortex as a result of thalamic circuitry (Bröcher et al., 1992; Wang & McCormick, 1993). Heterogeneous effects depend on structure, functional state and stimulus condition. For instance, the electric stimulation of nucleus basalis magnocellularis or mesencephalic nucleus cuneiformis affect the rat flash-evoked cortical responses (VEP) differentially, while the nucleus basalis modulates the early and late components of VEP, depending on the stimulus intensity and temporal rate of stimulation (Bringmann & Klingberg, 1989). It should also be emphasised that the action of ACh-agonists or antagonists on cortical neurons appears to be state-dependent (Kirby et al., 1986; Arakawa et al., 1993), as indicated by the diverging action of anesthetics on excitatory and inhibitory neurons in the visual thalamus (Pape & Eysel, 1988).

Conspicuously, several known modalities of ACh action at a cellular level or on neuronal (sub)systems appear consistent with the effects of ACh agonists/antagonists on the visual responses, as these are recorded by macroelectrodes in animals or in man. This congruity allows research on (ACh function in) vision to encompass a wide range of experimental approaches from in vitro models to clinical studies, with comparable methods and comprehensible results. Retinal electrophysiology is an example in this regard. Discrepancies among studies are likely to reflect dissimilarities in the experimental conditions (especially in the physical properties of stimulus) (Bodis-Wollner et al., 1986) or to depend on functional interactions with other neurotransmitter–receptor systems (e.g. Imamura & Kasamatsu, 1989; Daniels et al., 1994). Scopolamine has been used as a pharmacological model to study ACh-dependent visual functions. Its acute administration to healthy subjects affects the "late" waves (P2 and N3) of cortical responses to luminance (flash-VEP) (Fig. 1), while exerting negligible effects on VEP to patterned stimulation under stimulus conditions yielding minimal variations of luminance (Bajalan et al., 1986; Sannita et al., 1993;

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*The term "signal-to-noise ratio" or "signal-to-background ratio" is ambiguous in this context. Background spontaneous activity of neurons is unstationary and incompletely defined as a signal; it may be regarded as functionally irrelevant ("noise") in respect to stimulus-related events, but conceivably also reflects a role in the modulation of the response of target neurons (Ryan, 1989). "Signal-to-noise ratio" or comparable definitions have been used elsewhere (e.g. Sato et al., 1987a) and are used here in a practical sense and with due approximation.
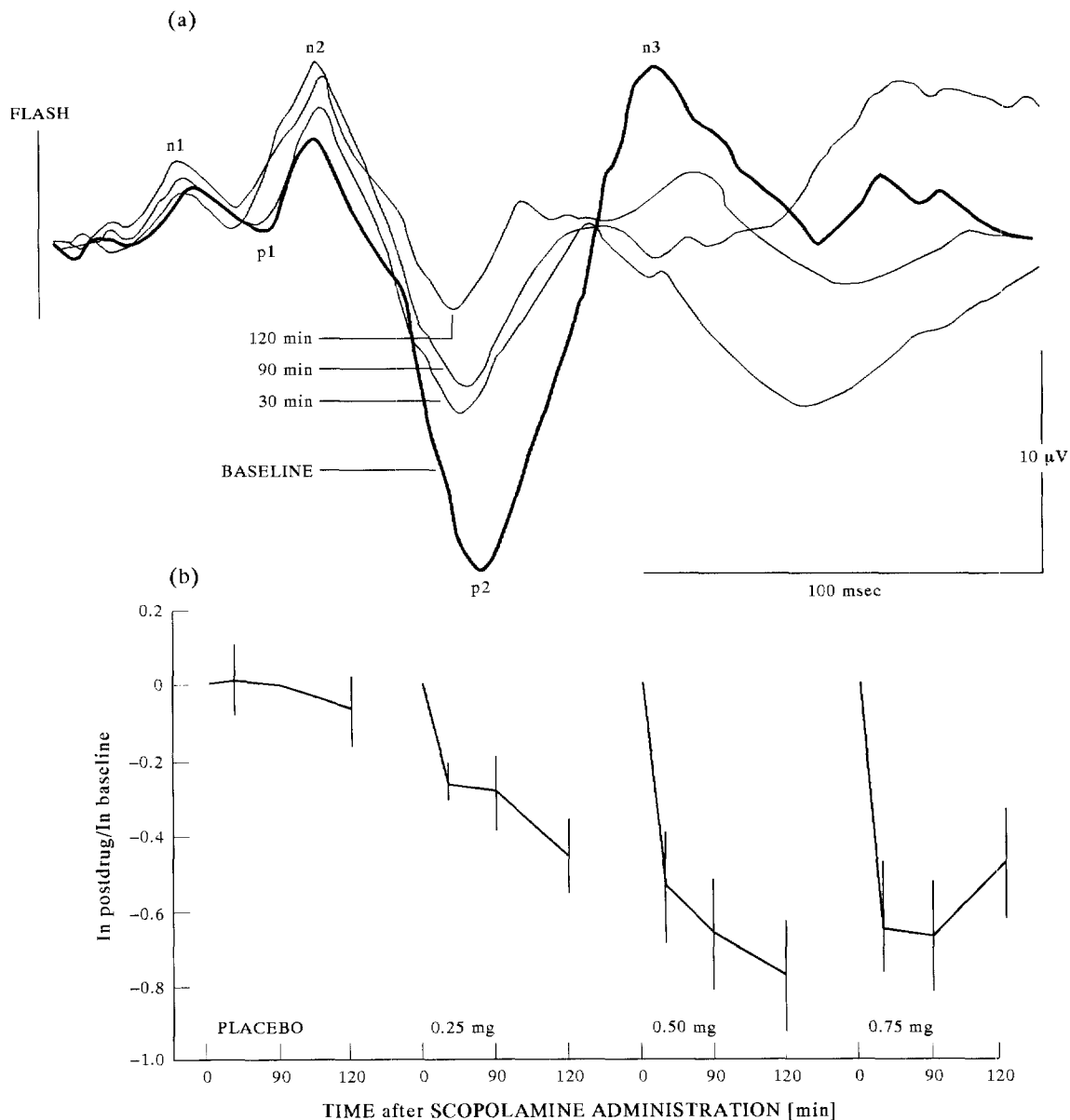
FIGURE 1. (a) Flash-VEP recorded from a young healthy volunteer in baseline condition (thick line) and after acute intramuscular administration of scopolamine, 0.50 mg (thin lines). The amplitudes of waves P2 and N3 are significantly reduced, while wave N2 is enhanced. (b) Postdrug differences from baseline of the P2-N3 amplitude; mean across subjects and standard error after log transformation. The P2-N3 amplitude (8.9-32.1 μV in baseline; mean 20.6 $\pm$ 5.3 μV) was reduced (25-80% of the corresponding baseline value; approximately 0.15-1.3 log units) in all 10 young healthy subjects to whom scopolamine was administered at doses of 0.25-0.75 mg. Postdrug values at any administered dose were significantly different from both baseline determinations and the corresponding placebo at each postdrug control (at levels ranging from $P < 0.02$ to $P < 0.0001$; paired t-test). Maximum reduction was at 90-120 min from administration depending on dose. Amplitude changes after placebo were never consistent across subjects or significant compared with baseline. The reduction of P2-N3 amplitude proved dose-related (regression analysis; $P < 0.00001$). The increase of wave N2 amplitude was observed in five subjects. Right eye stimulation; electrode derivation: O2-Fpz.

Ray et al., 1991; Daniels et al., 1994). Reduced amplitude is the prominent effect at doses compatible with substantial receptor occupancy (Sannita, 1995; Sannita et al., 1993), and occurs with temporal dynamics that parallel the estimated [C^{11}]scopolamine kinetics in man (Frey et al., 1992). This amplitude reduction proved independent of drug-induced modifications of background EEG (therefore suggesting a possible change in the "signal-to-noise ratio") and the magnitude of this effect is a function of baseline VEP amplitude, i.e. it is greater for predrug VEP of larger amplitude than for those of lower amplitude (Sannita, 1995; Sannita et al., 1993) (Fig. 1, Fig. 2). This latter finding is in agreement with comparable observations in parkinsonian patients treated with L-DOPA (Stanzione et al., 1991) and with reports of acute scopolamine affecting the VEP of young volunteers, but not those of DAT patients with impaired ACh function (Ray et al., 1991). It should also be noted in
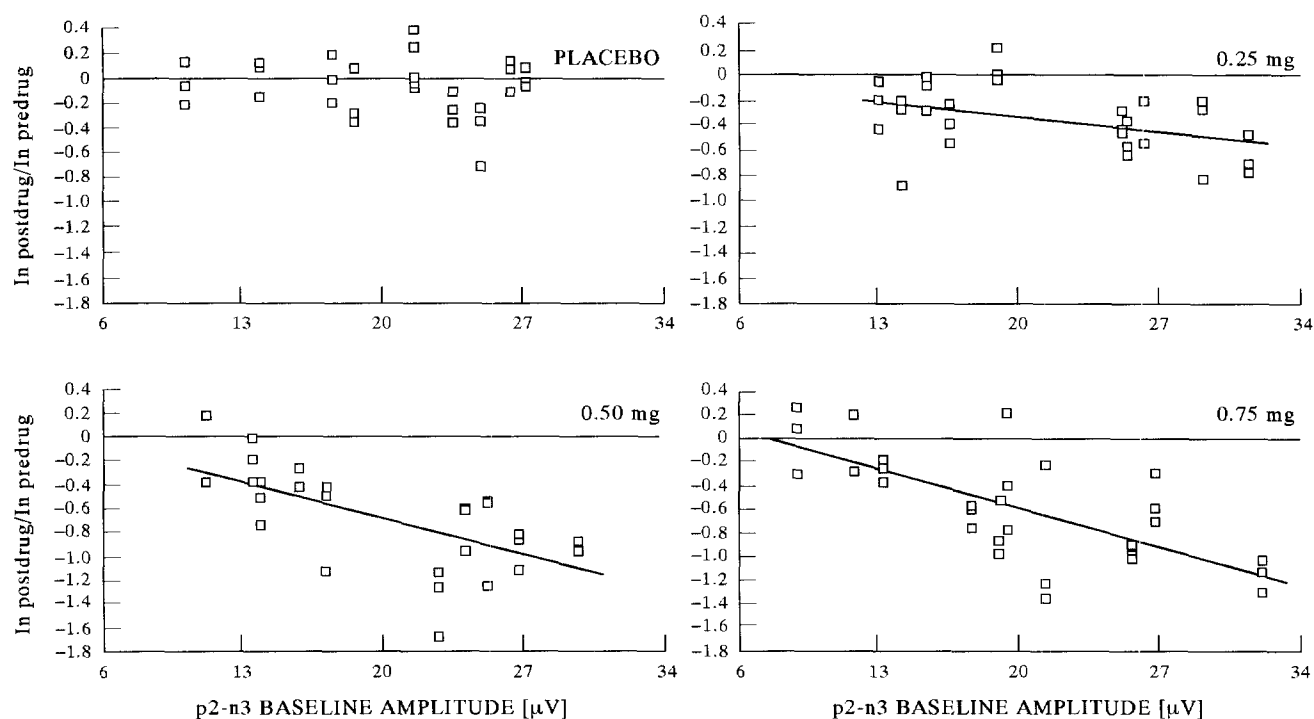
FIGURE 2. P2–N3 amplitude. Correlation between baseline values and the postdrug differences from baseline after placebo or scopolamine at any administered dose. Linear regression analysis at each dose; 0.25 mg: slope = −0.015, t = 2.167, P < 0.05; 0.50 mg: slope = −0.039, t = −4.338, P < 0.0001; 0.75 mg: slope = −0.042, t = −4.414, P < 0.0001). Linear regression analysis across doses: t = −4.494, P < 0.0001. The increase of wave N2 amplitude was not correlated with the baseline values before scopolamine administration as the P2–N3 amplitude was. Right eye stimulation; electrode derivation: O2–Fpz.

this regard that the interfering effect of scopolamine on cognitive functions has been described in DAT patients at lower doses than in age-matched controls (Sunderland *et al.*, 1987). Opposite changes (namely increased amplitude of flash-VEP "late" waves in the absence of sizeable effect on pattern-VEP) were induced under comparable experimental conditions by the acetylcholinesterase inhibitor galanthamine administered to healthy volunteers (Holl *et al.*, 1992) and by physostigmine in cats (Arakawa *et al.*, 1993). Some ACh-specificity of the mechanisms modulating "late" components of the VEP is indicated in the same studies (Holl *et al.*, 1992; Arakawa *et al.*, 1993; Sannita, 1995); consistent with such a result is the evidence that distinct structures and neurotransmission systems eventually combine to generate and modulate the VEP components. In this respect, "earlier" (e.g. flash-VEP P1 and N2 and pattern-VEP P100) and "later" (e.g. flash-VEP P2 and N3) waves are (over)-schematically suggested to reflect information processing in striate and extrastriate structures differentially (Schwartz & Cheney, 1966; Jeffreys & Axford, 1972; Maier *et al.*, 1987; Regan, 1989; Wright *et al.*, 1987).

The amplitude of P1 and N2 waves of flash-VEP reportedly increase in healthy volunteers after scopolamine (Sannita *et al.*, 1993) and decrease systematically in the cat after physostigmine (Arakawa *et al.*, 1993). A fast, GABA-mediated action of ACh on cortical cells (Müller & Singer, 1989) may account for this effect, as also suggested by the increase of the early VEP waves after

administration of GABA antagonist bicuculline in the cat (Zemon *et al.*, 1980). Interaction between cortical–subcortical ACh modulation and the carrier systems that mediate in the transfer of sensory information to and within the sensory cortex (e.g. stimulus-related oscillatory potentials) (Singer, 1993; Jefferys *et al.*, 1996) and are a suggested mechanism of higher brain function (Ribary *et al.*, 1995) has been recently postulated. Preliminary human data indicate that scopolamine increases the synchronization of the cortical oscillatory response to full-field luminance stimulation, while reducing it when single spots of small diameter (1–3 cm) serve as the stimulus (Lopez *et al.*, 1996). This observation may implicate some local ACh control in the cortex eventually resembling that of dopamine in the retina (Mangel & Dowling, 1985; Bodis-Wollner, 1990).

ACH DYSFUNCTION IN (ALZHEIMER'S TYPE) DEMENTIA

Substantial pharmacological evidence has steadily accumulated over two decades suggesting some role of ACh-mediated brain circuitry in higher brain function (e.g., learning, memory and cognition) and a preponderant impairment in Alzheimer's dementia of the cholinergic subcortical systems projecting to the cortex (Steriade & Biesold, 1990; Fibiger, 1991; Mesulam, 1995; Reiner & Fibiger, 1995, for references). In this respect, DAT is often labelled as a disorder of cholinergic innervation to

the cortex. Electrophysiological observations at increasing levels of neuronal organization (from single cell to event-related potentials) appear quite consistent in suggesting a common role of ACh in sensory (visual) information processing and cognition (Bartus et al., 1982; Kopelman & Corn, 1988; Muir et al., 1993). Single-cell studies in monkeys indicate sensitivity of cholinergic neurons of the nucleus basalis to stimuli that are novel or otherwise of behavioral relevance (Wilson & Rolls, 1990); this observation adds an essential feature to any model of ACh function. Cholinergic modulation of event-related potentials (e.g. originating upon the significant convergence, interaction, association or omission, or uneven incidence of events or sensory stimuli, such as the P300) has been documented in man and nonhuman primates. ACh agonists and antagonists affect visual P300 and visual processing in parallel, with qualitatively opposite effects (Hammond et al., 1987; Wilson & Rolls, 1990; Brandeis et al., 1992; Stanzione et al., 1991; Antal et al., 1993, 1994). Intraventricular administration of physostigmine and intracortical neural grafts of embryonic basal forebrain cells reverse the impairment of visual attentional performance induced by administration of the choline uptake blocker hemicholium or by quisqualate lesions of the basal forebrain (Muir et al., 1992). Cholinergic grafts in the neocortex or hippocampus of rats or monkeys partially restore a variety of functional deficits (including the more complex discrimination learning tasks suitable for primates) that are associated with experimentally induced lesions or aging (Dunnett, 1991; Ridley & Baker, 1991; Ridley et al., 1994), provided that appropriate interaction between grafts and host tissue is achieved. Recovery after neural transplant appears to depend upon cholinergic reinnervation and replacement (Dunnett, 1991; Nilsson et al., 1987) and the potential use in DAT treatment therefore depends on the functional specificity of ACh impoverishment in this disease.

VISION AND ALZHEIMER'S DEMENTIA

Both temporal and spatial functional visual modes are significantly impaired in Alzheimer's dementia (Celesia et al., 1993; Tobimatsu et al., 1994). Though widespread, neuronal degeneration in DAT is prevalent in the neocortex, hippocampus, and subcortical cholinergic structures projecting to the cortex, such as the basal forebrain. However, these neuronal networks are affected by DAT with significant differences in topography and evolution that eventually result in qualitatively different clinical and pathophysiological conditions; such differences may be particularly evident in the early stages of the disease (Whitehouse et al., 1983; Coyle et al., 1983). Neuropathological and histochemical studies have shown differences in the distribution of tau proteins in the retina and brain and an age-related increase of the immunoreactivity of amyloid precursor protein in ganglion cells of the elderly (Loffler et al., 1995). A significantly increased level of MHC cell II expression was detected in the retinas of DAT in the absence of lymphocytic infiltrates

(Liew et al., 1994), therefore suggesting that the pathogenesis of Alzheimer's disease as observable in the retina may be distinct from that observed in some brain areas. Neuronal degeneration is reportedly less severe in the retina, optic nerve, geniculostriate pathway, primary visual cortex and corticocortical outflow from area 17 than it is in visual associative areas (Mountjoy et al., 1983; Morrison et al., 1991; Lewis et al., 1987; Hof & Morrison, 1990; Rizzo et al., 1992). Accordingly, visual dysfunction includes deficits in color discrimination (notably tritanomalus) and impairment of spatial and temporal resolution, stereoacuity, visual acuity, contrast sensitivity (especially at low frequencies), visuospatial functions, (homogeneous and pattern) backward masking, etc. Significant, central and peripheral reductions in global sensitivity were detected in DAT by visual field topography, while no significant change in the critical flicker-fusion frequency or evidence of retinocalcarine abnormality specific to DAT have been reported (Cronin-Golomb et al., 1991, 1993, 1995; Uhlmann et al., 1991; Bassi et al., 1993; Hutton et al., 1993; Wolin, 1994; Kaskie & Storandt, 1995; Filoteo et al., 1995; Trick et al., 1995; Butter et al., 1996).

Remarkably, visual impairment seems to have a prominent functional impact on specific cognitive domains in DAT and to significantly predict the risk and clinical severity of cognitive dysfunction, although the progression of cognitive decline appears unpredictable on the basis of visual dysfunction (Uhlmann et al., 1991; Cronin-Golomb, 1995; Cronin-Golomb et al., 1995). In this respect, visual impairment as it is observed in DAT is suggested to be mostly cortical and to reflect the loss of corticocortical systems (with "visual disconnection" involving e.g. peristriate and inferotemporal visual cortices) rather than retinal or optic nerve damage (Cronin-Golomb et al., 1991, 1993; Morrison et al., 1991; Hof & Bouras, 1991). This view is consistent with the DAT patients demonstrating visuospatial deficits or impaired performance in visual cognitive tasks as often as, or more often than, they are found to have impaired elementary visual functions. The patients' complaints have generally been understood as reflecting cognitive impairment and dysfunction resulting from pathology affecting the associative rather than the primary visual areas (Brun & Englund, 1981; Mountjoy et al., 1983; Mendez et al., 1990; Parasuraman et al., 1992; Kaskie & Storandt, 1995). DAT patients whose flash- and pattern-VEP were within the normal range were found to perform poorly in visual and memory tasks compared with controls (Mielke et al., 1995). Reduced regional glucose metabolic rate in both primary and secondary visual cortices was observed in these patients; however, their psychometric performance in visual tasks correlated with glucose rate reduction in secondary but not in primary visual cortex (Mielke et al., 1995). Based on these observations and on the described correlation between VEP alteration and disease severity, the observation of abnormal waves P2 and N3 ("late") of flash-VEP in the absence of sizeable alterations of earlier waves and of the

pattern-VEP was given relevance in the diagnosis of DAT, as being indicative of progressive (ACh-related) impairment in visual associative areas (Wright *et al.*, 1987; Philpot *et al.*, 1990; Brodie *et al.*, 1992; Rizzo *et al.*, 1992; Daniels *et al.*, 1994). This hypothesis appears congruent with the suggested dichotomy of earlier and later components of cortical responses and with the effect of ACh agonists/antagonists on these waves (Wright *et al.*, 1987; Philpot *et al.*, 1990; Swanwick *et al.*, 1996).

The real scenario of visual impairment in DAT, however, is more complex than the above summary would suggest. The extent to which the electrophysiological observations allegedly indicating DAT actually reflect ACh impoverishment and differential striate/ extrastriate impairment remains unclear. Electrophysiological studies indicate that both primary and secondary auditory cortical functions are impaired in demented patients and suggest associated dysfunction of the reticular activating system (O'Mahony *et al.*, 1994). Similarly, patients with even mild DAT display several abnormal visual features attributable only in part to cognitive deterioration (Sekuler *et al.*, 1980; Schlotterer *et al.*, 1984; Nissen *et al.*, 1985). Significant damage in the retina and retinocortical pathway has been also described (Hinton *et al.*, 1986; Trick *et al.*, 1989; Bassi *et al.*, 1987; Tsai *et al.*, 1991; Brodie *et al.*, 1992). Notably, morphometric analyses in DAT patients indicate a significant (approximately 50% on average compared with age-matched controls) reduction in number and density of ganglion cells and ganglion cell axons that is selective for large ganglion cells (with soma perimeter of approximately 35–60 μm). A disproportionate (or earlier) degeneration in the type A ganglion cells and the magnocellular pathway has been suggested and appears plausible (Hinton *et al.*, 1986; Bassi *et al.*, 1987; Sadun & Bassi, 1990). Accordingly, widespread neuronal degeneration of the magnocellular layer of LGN has been observed (Johnson *et al.*, 1987). These morphometric observations were matched by electrophysiological investigation (pattern-ERG) under experimental conditions minimizing contribution from the p-cells (Barris *et al.*, 1988; Trick *et al.*, 1989). The results obtained suggest altered parallel processing and appear consistent with the observed discrepancies between VEP responses to flash or patterned stimulation to the extent these stimuli may trigger the m- and p-pathways differentially. However, ERG alterations proved restricted to the steady-state pattern-ERG in a group of patients with Alzheimer's disease (Nesher & Trick, 1991), while the ERG responses to both pattern and flash stimuli were reportedly normal in a group of DAT patients (Strenn *et al.*, 1991).

The existing inconsistencies among studies may depend on methodological differences e.g., of the physical characteristics (spatial frequency, contrast, adaptation, luminance, etc.) of stimuli used to test visual function (Bodis-Wollner *et al.*, 1986). Whether DAT-related changes in the visual system are qualitatively different from those that occur spontaneously during aging or whether these are enhanced in DAT also remains

to be defined. Contingent abnormalities of retina, LGN, visual pathways, and cortex need to be taken into account as well, when trying to comprehend the pathophysiological processes underlying visual impairment in DAT and in the attempt to identify disease-specific abnormalities. Age-related loss of ganglion cells, for instance, was observed in non-demented subjects (Dolman *et al.*, 1980; Balazsi *et al.*, 1984), but was not reported for the control group in the study by Sadun & Bassi (1990). Curcio & Drucker (1993) did not observe any evidence for substantial reduction in ganglion cell density within the central 43 deg of the visual field in DAT patients compared with age-matched controls; the density of ganglion cells subserving the central 11 deg of vision, by contrast, was reduced in both DAT and aged controls compared with retinas from young adults. Aging effects may be a confounding variable in retinal and cortical electrophysiology (Peterson, 1968; Weleber, 1981; Allison *et al.*, 1984; Trick *et al.*, 1985; Celesia *et al.*, 1987; Schoon *et al.*, 1989; Sannita *et al.*, 1989); complex trends of variation throughout the entire life span (from childhood to senescence) were described to depend on gender or stimulus condition, to differ among ERG/VEP individual waves, and conceivably also to reflect interactions of metabolic and hormonal factors (Peterson, 1968; Allison *et al.*, 1984; Sannita *et al.*, 1989).

In general, DAT-related abnormalities in the visual system are as multiform as the disease itself and conceivably reflect individual differences as well as dissimilarities in the rate of progression (see e.g. Butters *et al.*, 1996), that eventually may lead to peculiar clinical variants dominated by visual disturbances (Levine *et al.*, 1993; Graff-Radford *et al.*, 1993) or to conditions with overlapping visual dysfunction due to aging or DAT. Despite the available evidence, the clinical or physiological (visual) "markers" of Alzheimer's dementia and predictors of disease progression and severity still remain to be defined.

COMMENTS, CRITIQUE AND WORKING HYPOTHESES

A coordinated role of ACh in neuromodulation appears established and models matching the available physiological evidence have been contrived. In this framework, ACh would improve the "signal-to-background ratio" of ACh-facilitated cells and prevent activation of neurons not receiving afferent input, while enhancing synaptic interconnections among cells receiving input (Hasselmo & Bower, 1993). This mechanism would suit to some extent both sensory and cognitive processes and provides possible ways to understand storage, retrieval and association of complex patterns of neuronal activity in the brain. There is hardly any question that pharmacologically induced impairment of ACh brain activity may affect higher brain functions with characteristics comparable with those of Alzheimer's dementia (e.g. Baker & Giacobini, 1988; Christensen *et al.*, 1992). However, experimental studies failed to provide valid proof of a behavioral role of cortical cholinergic afferents from the

basal forebrain (Everitt *et al.*, 1987; Robbins *et al.*, 1989). Accordingly, the specificity of ACh action in cognition is still unproven and the agonist/antagonist muscarinic model appears questionable (Oken *et al.*, 1994). Many nonspecific endogenous aspects of cognitive functions (e.g., arousal, attention, alertness) are tonically modulated by several neurotransmitter systems projecting to the cortex (Foote, 1987; McCormick, 1989; Steriade *et al.*, 1993; Oken *et al.*, 1996). Therefore, it would be simplistic to underestimate the existing functional interactions among both cholinergic and noncholinergic neurotransmitter/receptor systems or neuronal and non-neuronal (metabolic, neuroendocrine) factors and their impairment as it occurs in DAT and in other pathological conditions.

In spite of the increasing sophistication of unitary models (Ridley *et al.*, 1991; Sarter & Bruno, 1994), there are serious limitations to the hypothesis of selective ACh-related brain malfunctioning leading to dementia. These are the widespread cholinergic innervation of nearly the entire CNS and the observation that ACh release following neuronal activation varies considerably depending on procedural, situational and, largely, "behavioral" conditions (Fibiger, 1991; Pineda, 1995). Positron emission tomography studies in man (Frey *et al.*, 1992) also showed local differences (in kinetics, affinity and distribution) of ACh cortical receptors, with distinct topographic and laminar patterns. This heterogeneous distribution should be expected to serve functional purposes rather than being casual. However, no "functional anatomy" of cognitive processes has been tentatively outlined to match it (Fibiger, 1991; Sarter & Bruno, 1994), and whatever the specific cholinergic dysfunction resulting in cognitive impairment in DAT may be, its identity remains unknown. The concept itself of DAT as simply resulting from impoverished muscarinic transmission is contradicted by data suggesting some higher degree of complexity of brain impairment. Post-mortem samples of DAT patients show unchanged numbers of cortical postsynaptic muscarine receptors (Mash *et al.*, 1985; Flynn *et al.*, 1991). By contrast, substantial qualitative regional changes have been documented in receptor affinity, receptor subtypes and receptor-G protein, while abnormalities in membrane composition have been described in both age-related diseases and DAT. These changes result in abnormal coupling and affinity properties and therefore in receptor inability to form, or shift from, high affinity agonist binding sites; as well as in defective postsynaptic signal transduction (Flynn *et al.*, 1991; Svensson *et al.*, 1992; Ladner *et al.*, 1995; Roth *et al.*, 1995). It should be noted in this regard that cholinergic neurons conspicuously use choline both to produce ACh and to synthesize membrane phosphatidylcholine (Wurtman, 1992). The hypothesis that altered membrane composition may be a primary cause of the cellular abnormalities resulting in impaired signal transduction and DAT needs to be tested. Accordingly, the potentialities of molecular biology of

ACh receptors in providing future therapeutic tools need to be verified.

Diseases other than DAT (e.g. familial olivoponto-cerebellar atrophy—OPCA) can cause a loss of ACh neurons as prominent as that which occurs in clinically disabling DAT. The resulting cognitive impairment, though qualitatively similar, is, however, less disabling in OPCA than in DAT and has different neuropsychological features (Kish *et al.*, 1988). In this respect, memory defects in DAT may therefore depend on hippocampal degeneration (i.e., on the loss of function-dedicated structures) rather than reflect inadequate ACh availability at selective sites of action. This hypothesis is also supported by recent findings of the association of apolipoprotein E ε4 allele with medial temporal lobe atrophy and memory impairment in both DAT patients and non-demented elderly subjects (Soininen & Riekkinen, 1996). Based upon these considerations, DAT stands as a heterogeneous disease and the role of ACh in memory processes appears restricted to facilitation of nonspecific functional characteristics of neurons (e.g., suppression of normal adaptation of pyramidal cell firing; long-term potentiation; reduced interference from collateral synapses) (Hasselmo & Bower, 1993). The evidence of the multifactorial pathogenesis of DAT contrasts with the scopolamine/physostigmine model of cognitive impairment and dementia (Fibiger, 1991) and the therapeutic rationale derived from it (Baker & Giacobini, 1988). Accordingly, substitutive treatments attempting to restore cognitive function in demented patients by means of compounds enhancing ACh availability or activating cholinergic function have been thus far disappointing (Flynn *et al.*, 1991). Transplantation of fetal brain tissue rich in cholinergic neurons is now foreseen as an unpromising therapeutic approach compared with the promise of fetal transplantation in Parkinson's disease (Dunnett, 1991; Olanow *et al.*, 1996). The future potentialities of grafting genetically modified cells onto the brain (Gage *et al.*, 1987) will depend on the identification of genetic abnormalities peculiar to DAT, rather than aiming at counterbalancing ACh loss (Dunnett, 1991).

There is no evidence of a peculiar action of ACh in visual cortex. The specificity of cholinergic function in vision, therefore, should be regarded as inferential, especially when considering both the multiplicity of VEP generators and how little is understood about the neuronal basis and neuromodulation of visual function. ACh has been reported to depress neuronal responses to nonpreferred stimulus directions while enhancing responses to the preferential direction (Sillito & Kemp, 1983). This observation, however, is questioned by experimental data (e.g., Sato *et al.*, 1987a,b; Müller & Singer, 1989) suggesting that ACh facilitates the firing of cells irrespective of stimulus properties, much as cholinergic neurons in nucleus basalis are facilitated by ACh when responding to novel stimuli (Wilson & Rolls, 1990). To a good approximation, the modulatory effect of subcortical ACh structures on cortex appears nonspecific

as well. However, some ACh-specificity needs to be contrived, if the available evidence persistently supporting it in the retina, LGN and visual cortex is taken into account. Electrophysiological observations at different levels of neuronal complexity appear congruent in this regard (Ikeda & Sheardown, 1982; Ariel & Daw, 1982; Kirby et al., 1986; Sato et al., 1987a,b; Schmidt et al., 1987; Müller & Singer, 1989; McCormick, 1989, 1990; Sannita et al., 1993; Sannita, 1995; Jurklies et al., 1996). A practicable hypothesis would be that ACh action becomes function-specific as a direct consequence of the architecture of special-purpose brain (micro- or macro-) circuits dedicated to visual information processing in which it functions. This would properly suit the concept of neural circuitry as a template of function, i.e., a mechanism transforming simple discrete events into complex activity. Such a concept is fundamental for neural network modelling and is supported by intriguing parallelisms in architecture and operation between some artificial networks for distributed pattern recognition/association and the cerebral cortex they are attempting to model (e.g. Anderson & Rosenfeld, 1988; Haberly & Bower, 1989). The olfactory cortex is an example in this regard of a model circuit for the study of olfaction and, largely, of (associative) memory (Haberly & Bower, 1989; Nakanishi, 1995). It should be noted that remarkable similarities exist in the organization of the retina and olfactory bulb, as well as in the receptor and (second-order) neuron mechanisms of information processing in the visual and olfactory systems (Nakanishi, 1995). This conceptual framework may be extended to the functional interpretation of the visual cortex as well, though at different levels of sophistication of the neuronal organization. A specific role for ACh can be devised as a regulator of mechanisms determined by structure and triggered by sensory input, owing to the strict correlation between neural circuitry and function that is a prominent feature in the visual system.

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