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Midlatency auditory evoked responses: differential abnormality of P1 in Alzheimer's disease

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Summary The human 'P1' middle latency evoked potential is postulated to be generated in the thalamus by a cholinergic component of the ascending reticular activating system. To test the hypothesis that P1 and its generator substrate are abnormal in Alzheimer's disease (AD), a disorder of marked cholinergic deficiency, recordings of middle latency responses to click stimuli were carried out. Comparisons between the AD and age-matched control groups indicated normal auditory brain-stem and Pa responses but a significant decrease in P1 amplitude. This P1 abnormality suggests that the midbrain cholinergic cells in AD may be dysfunctional.

Key words: Midlatency auditory evoked responses; Alzheimer's disease; Ascending reticular system; Cholinergic brain-stem system; P1 abnormality

Alzheimer's disease (AD), the single most common cause of cognitive impairment in the elderly, lacks pathognomic laboratory tests and the disorder must currently be diagnosed by clinical criteria, pending the examination of brain tissue, usually at autopsy. Electrophysiologic measures of particular brain systems, however, can provide non-invasive probes of brain dysfunction as an adjunct to clinical diagnosis and putative treatment. Because cholinergic cells of the basal forebrain system show marked degeneration in AD (Terry and Davies 1980; Whitehouse et al. 1981; Bartus et al. 1982; Price et al. 1982), we postulated that cholinergic cells of the midbrain might likewise be dysfunctional. Abnormal cholinergic cells of the midbrain would be predicted to result in an abnormal P1 response, in light of the background data summarized below.

The scalp-recorded human 'P1,' a 50–65 msec positive potential (Picton et al. 1974), decreases and disappears as click rates exceed 1/sec, a recovery cycle characteristic also shown by the cat middle latency 'wave A,' but not shown by any of the preceding auditory evoked response components in either species (Buchwald et al. 1981; Hinman and Buchwald 1983; Erwin and Buchwald 1986a; Erwin and Buchwald 1987). In studies of sleep-wakefulness, the human P1 and the cat wave A were both found to decrease and disappear during slow wave sleep (SWS) and to increase dramatically during rapid eye movement (REM) sleep to an amplitude similar to that during wakefulness (Chen and Buchwald 1986; Erwin and Buchwald 1986b). None of the preceding or succeeding evoked potentials in either species showed similar changes.

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The prolonged recovery cycle and the amplitude changes linked to states of sleep and arousal uniquely shown by the human P1 and cat wave A suggest that those responses reflect a generator substrate within the arousal system of the ascending reticular formation. This hypothesis was supported in the cat by long-term studies following hemispherectomy, i.e., bilateral removal of neocortex, basal ganglia and limbic lobes (Buchwald et al. 1981; Hinman and Buchwald 1983; Erwin and Buchwald 1987). Wave A was not abolished, proving that its generation depended upon some system within the brain-stem-diencephalon. In the intact, awake cat, depth mapping studies in the brain-stem and diencephalon localized single units and field potentials with similar latency, recovery cycle characteristics, and wave form as the surface wave A (Buchwald et al. 1981; Hinman and Buchwald 1983; Erwin and Buchwald 1987). A trajectory, which extended from the lateral midbrain area of the pedunculo-pontine-tegmental nucleus to the intralaminar thalamus, defined the course of those depth responses and indicated a generator substrate for wave A within the ascending reticular activating system (RAS). Other studies have shown that units bordering and within the pedunculo-pontine-tegmental nucleus decrease in firing frequency during SWS and significantly increase in firing frequency during REM sleep (summarized in Erwin and Buchwald 1986a), consistent with the finding that the surface recorded wave A disappears during SWS and reappears during REM sleep. These data suggest that wave A provides an electrophysiological probe of tonic RAS activity. Moreover, the general similarities in recovery cycle and sleep-wake cycle characteristics between this animal model and the human P1 suggest that these components may share similar generator substrates.

All of the brain-stem cholinergic cells with forebrain projections are clustered within the pedunculo-pontine-tegmental (and adjacent dorsolateral tegmental) nucleus, as quantified by choline acetyltransferase (CAT) immunohistochemistry (Shute and Lewis 1967; Armstrong et al. 1983; Satoh et al. 1983; Woolf and Butcher 1986). Furthermore, the trajectory of the wave A system, described above, corresponds to the distribution of the dorsal tegmental cholinergic pathway (Shute and Lewis 1967; Armstrong et al. 1983; Satoh et al. 1983; Woolf and Butcher 1986).

Recent experiments have shown that destruction of these cholinergic cells of the pedunculopontine nucleus or injections of scopolamine, a postsynaptic (muscarinic receptor) blocker of cholinergic transmission, blocks wave A generation without effect on the preceding auditory evoked responses (Dickerson et al. 1986; Harrison et al. 1988). The cat wave A thus appears to be produced by cholinergic activation of target thalamic neurons. In the human, a recent case study suggests that a low dose of scopolamine administered transdermally also results in the diminution of P1 without effect on the preceding potentials (Buchwald in press).

Taken together, such data support a hypothesis that the cat wave A and the human P1 are generated within the ascending RAS by presynaptic cholinergic (CAT positive) cells in the midbrain area of the pedunculo-pontine-tegmental nucleus projecting to postsynaptic cholinoceptive (muscarinic) cells in the intralaminar thalamus. Insofar as forebrain cholinergic dysfunction occurs in AD, the foregoing data led us to postulate that the midbrain cholinergic cells might likewise become dysfunctional and the P1 abnormal in AD. In order to test this prediction, the following study was carried out.

Procedures

Subjects included a comparison group of 10 healthy men (age 39–57, mean 47 years), an age-matched control group of 6 healthy men (age 57–74, mean 64 years) who were neuropsychiatrically normal, and 6 men (age 53–75, mean 63.2 years) with definite (N = 4) or probable (N = 2) AD. Probable AD was diagnosed somewhat more stringently than NINCDS-ADRDA guidelines (McKhann et al. 1984) and we required that patients have progressive difficulties in memory, language, visual-spatial skills, cognition and personality and be without features atypical for AD, including irregular course, major depression, focal neurologic findings or extrapyramidal symptoms

(Cummings and Benson 1983, 1986; Kempler et al. in press). Diagnoses in 4 patients were revised to definite AD following biopsy of right frontal cortex in which confirmatory plaques and neurofibrillary tangles were demonstrated. Patients were required to have mild to moderate dementia; they scored 0.5 or 1.0 on the Clinical Dementia Rating Scale (Hughes et al. 1982), and 16–20 (means 18.8) on the Minimental State Exam (Folstein et al. 1975). Three had definite family history for AD. Written informed consent was obtained from all subjects and each patient's spouse. Although a small sample, this group of AD patients represents a well-defined population: all were diagnosed and studied at approximately the same time, their diagnostic profiles were similar, and from 4 of the 6 the rarely available but conclusive neuropathological proof of AD was obtained.

Hearing thresholds and auditory brain-stem responses were obtained in all cases. In the standard condition, rarefaction 1/sec click stimuli (0.1 msec duration) were presented binaurally through Sony Nude earphones at an intensity 55 dB above hearing threshold for each subject. Recovery cycle studies utilized click rates of 0.5, 1, 5, 8, and 10/sec. All testing and recording were conducted in an electrically shielded and sound-dampened room. Evoked potentials were recorded from an electrode placed over a midline central (Cz) scalp location which was referenced to linked mastoid electrodes with gain settings of 200 K and filter bandpass settings of 10–300 Hz. Activity from eye electrodes (supraorbital and canthal positions) was amplified 10 K with a bandpass of 1–300 Hz and was used to monitor eye movements. All electrode impedances were maintained below 10 K throughout the experiment.

Prior to recording, the subject was seated comfortably and instructed to relax with eyes open. AD subjects were monitored by an observer who sat with the subject throughout the recording session. Stimuli were presented in blocks of 250 trials with a second replication block at 250 trials. Single trials were digitized at 500 μsec intervals over a 100 msec epoch (200 time points) following stimulus onset. To be consistent with the historical middle latency response (MLR) data generated in our own laboratory (Chen and Buchwald 1986; Erwin and Buchwald 1986a, b; Buchwald in press), as well as in other laboratories (Picton et al. 1974), Pa was defined as the maximum positive peak in the 25–40 msec latency range, P1 the maximum positive peak in the 50–65 msec latency range, and Nb the 40–50 negative deflection between Pa and P1. Two independent raters identified sites for peak measurements; amplitude voltages were referenced to a zero DC baseline. In the AD subjects, voltages in the 50–65 msec range of the P1 were often negative (*re*, 0 DC) and in these cases the least negative loci were selected for measurement.

Results

In Fig. 1A, the MLRs recorded from a 53-year-old definite AD subject are compared with those recorded from a 57-year-old normal male. While the Pa components are clearly visible in both subjects, the large P1 component in the normal male is clearly missing in the AD subject. In Fig. 1B, MLR grand averages for a group of normal males are compared with the AD group. As with the individual data, the AD group data show a Pa component with normal morphology and latency but there is virtually no P1.

The range of response variability across individual AD subjects is illustrated in Fig. 2, with the peak amplitude and latency measurements for both Pa and P1 presented in Table I. One-sided Mann-Whitney comparisons between the AD and age-matched control groups indicated a significant decrease in P1 amplitude ($P < 0.004$) but there were no significant group differences in Pa amplitude or latency.

In normal subjects the P1 recovery cycle is relatively long, so that the response diminishes and disappears as click rates exceed 1/sec (Erwin and Buchwald 1986a). We hypothesized that, in contrast to this normal rate effect, responses of abnormal generator cells might be recruited with faster click rates so as to produce a P1 response in the AD subjects. Thus, clicks were presented at rates of 0.5, 1, 5, 8, and 10/sec in random order, with a rest interval between each 250 trial block and with a second replication set using a different

random sequence. MLR grand averages of the AD subjects and age-matched controls at the different rates of stimulation are illustrated in Fig. 3. The more rapid click rates produced the expected P1 decrement in the controls, but did not recruit a P1 response in the AD subjects. The Pa component,

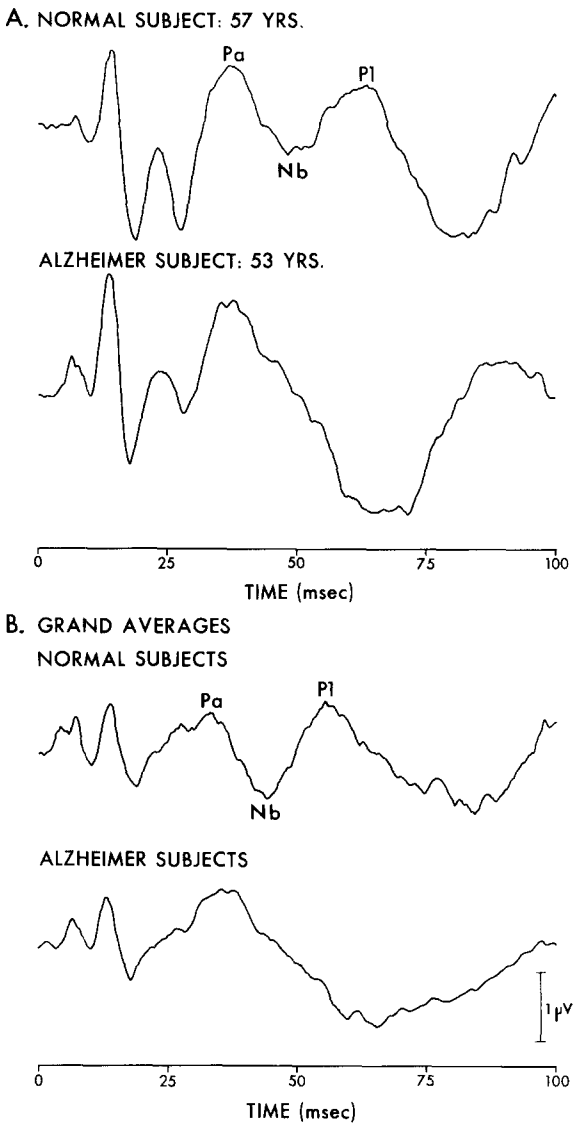

Fig. 1. Middle latency responses recorded from normal and AD subjects. All responses elicited by 1/sec click stimuli. Positivity is indicated by upward voltage deflections. A: normal male compared with a definite AD subject (500 trials/trace). B: grand averages of 10 normal males (39–57 years) and the 6 AD subjects (500 trials/subject).

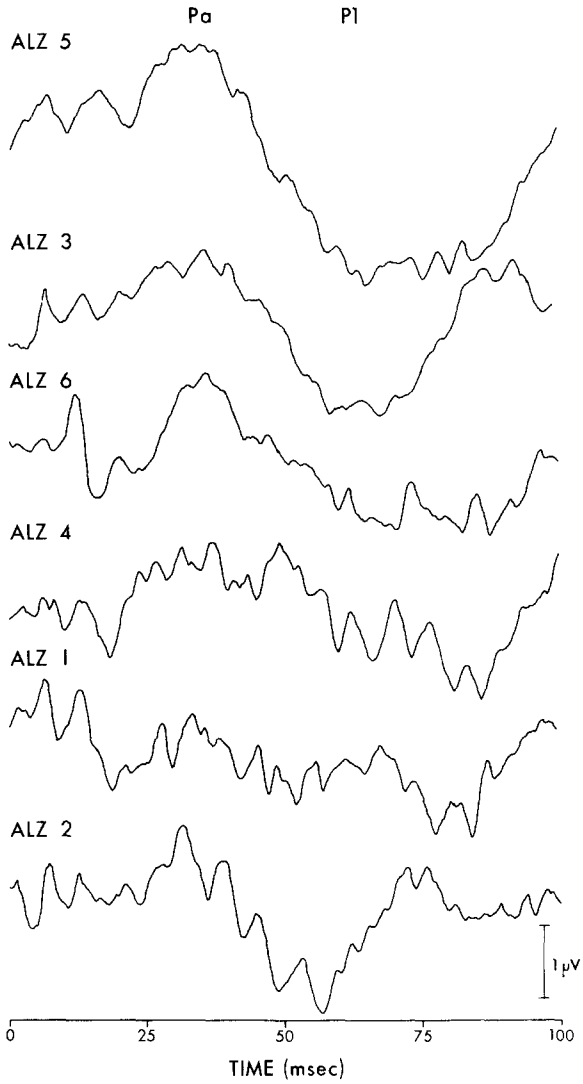

Fig. 2. MLRs of each AD subject (1/sec click stimuli, 500 trials/trace).

which was normal at slow click rates for both the control and AD subjects, showed stability and absence of change in both groups during the faster rates, as has been previously reported for normal adults (Erwin and Buchwald 1986a).

Discussion

The absence of P1 in these AD subjects does not reflect an inability to hear the click stimulus.

TABLE I

Peak amplitude and latency values for Pa and P1 components of control and AD subjects. Statistics were obtained from a 1-sided Mann-Whitney test comparing the 2 groups.

	Age (years)	Pa		P1	
		Latency (msec)	Amplitude (μV)	Latency [a] (msec)	Amplitude (μV)
Control subjects					
C01	57	26	0.49	51	0.34
C02	58	37	1.08	64	0.80
C03	63	29	0.83	51	0.65
C04	63	32	0.31	50	−0.25
C05	74	37	1.35	51	1.29
C06	69	28	0.92	53	1.08
Average	64	31.5	0.83	53.3	0.65
Alzheimer's disease subjects					
A01	62	33	0.46	56	−0.18
A02	62	32	1.08	53	−0.77
A03	53	35	1.08	65	−1.02
A04	63	31	0.77	56	0.15
A05	75	35	1.42	60	−1.42
A06	64	36	1.11	62	−0.46
Average	63.2	33.7 *	0.99 *	58.7	−0.62 ***

* NS differences between groups.

*** $P < 0.004$.

[a] Within the defined 50–65 msec latency range of the P1, loci of least negativity were selected for peak amplitude measurements when the voltage across this time period remained negative *re* 0 DC. Because AD P1 components were not clearly seen, in terms of large peak amplitudes, the latencies at which amplitude measurements were made are shown but were not used for statistical comparisons.

In only 1 individual was the hearing threshold slightly higher than normal and in all subjects the click stimulus was normalized to 55 dB HL. Moreover, auditory brain-stem responses were recorded from all subjects and the Pa component occurred at a normal amplitude and latency. As the AD subjects were monitored by an observer throughout all recordings and were consistently awake, with eyes open, P1 could not have disappeared because of sleep onset. Thus, we conclude that the P1 component is diminished or missing in the AD subjects because its generator substrate is abnormal.

While a number of clinical reports of subjects sustaining cortical lesions have focused upon possible generator origins of the Pa component, P1

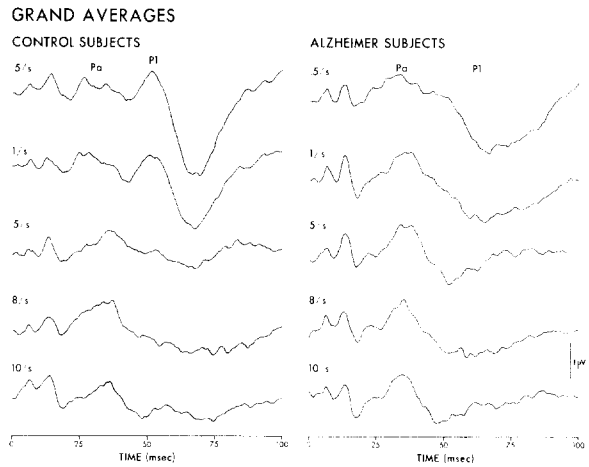

Fig. 3. Grand averages of the 6 age-matched control and AD subjects to increasing rates of click stimulation (500 trials/subject).

has generally not been discussed. Most of these lesion studies (Graham et al. 1980; Kraus et al. 1982; Özdamar et al. 1982; Rosati et al. 1982; Özdamar and Kraus 1983), as well as complementary topographic and parametric recordings (Pulleti and Celesia 1970; Lee et al. 1984; Erwin and Buchwald 1986a, 1987), suggest that Pa is generated by auditory cortex of the superior temporal gyrus (although 2 patients with temporal lesions have been reported to show no MLR abnormality (Parving et al. 1980; Woods et al. 1984)). A correlative electrophysiological and magnetic field study of the 'P50' potential likewise suggests a superior temporal gyrus, i.e., planum temporale, origin for this component (Reite et al. 1988). In this study, P50 occurred in a latency range somewhat longer than the usual peak latency of Pa but shorter than that of the P1. Because the relatively weaker monaural, in contrast to the usual binaural, stimulation and the wideband 4–300 Hz recording procedure may increase component latencies (Erwin and Buchwald 1986b), this P50 may be both parametrically and physiologically more similar to Pa than to P1. This interpretation would be consistent with the various studies cited above which suggest that Pa has its origins in temporal cortex.

Previous work in our laboratory on the cat and the human has closely linked the generator substrate of the P1 potential to the ascending reticular

activating system and to its relays in the intralaminar thalamus (Buchwald et al. 1981; Hinman and Buchwald 1983; Erwin and Buchwald 1987). More recent experiments have led to the hypothesis that this potential is generated by cells in the intralaminar thalamic nuclei which receive essential input from cholinergic cells of the midbrain reticular formation (Dickerson et al. 1986; Harrison et al. 1988; Buchwald in press). The present data are the first demonstration that the P1 component is abnormal in AD. Although the present sample is small, the results suggest that marked P1 abnormality may provide an ancillary diagnostic, or prognostic, tool in conjunction with other neuropsychological indices of Alzheimer's disease.

In light of the preceding and other experimental reports indicating midbrain neuropathology (Jacobs et al. 1986) and reduced REM sleep time (Prinz et al. 1982; Vitiello et al. 1984) in AD, a P1 abnormality suggests that the cholinergic cells in the midbrain of AD patients may be dysfunctional.

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