Electroencephalography and clinical Neurophysiology, 82 (1992) 445–452

EEG 91576

Effect of the cholinesterase inhibiting substance galanthamine on human EEG and visual evoked potentials

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(Accepted for publication: 25 November 1991)

Summary The action of galanthamine (GAL), a cholinesterase inhibiting substance, on resting EEG and on flash visual evoked potentials (VEPs) was tested in 9 healthy subjects. Alpha power was increased significantly in 4 of 8 subjects after the infusion of 10 mg, which provided a median inhibition of 47% of acetylcholinesterase in erythrocytes. Mean alpha frequency and peak alpha frequency decreased significantly in 5 of the 8 subjects by 0.22–0.98 Hz. Alpha power increase and alpha frequency decrease were not accompanied by changes in theta power.

The amplitudes of the late components of the flash VEP were increased in 8 of 9 subjects receiving doses of 10–35 mg of GAL, while the early components remained unaffected. Increase of late VEP components was significantly correlated with the strength of cholinesterase inhibition.

The synchronizing effect of GAL in these healthy volunteers obviously contrasts with the known desynchronizing effect of physostigmine in animal experiments.

Key words: Acetylcholinesterase inhibition; Electroencephalography; Galanthamine; Visual evoked potentials; (Human)

On the basis of reports detailing the cholinergic deficit in the brain of patients with senile dementia of Alzheimer's type (SDAT; Davies and Maloney 1976; Perry et al. 1977a, b) acetylcholinesterase (AChE) inhibition is frequently used in trials for the treatment of this disease (Drachmann et al. 1982; Thal et al. 1986; Summers et al. 1989). Since sufficient dosage is essential to successful therapy, acetylcholine (ACh) sensitive parameters of brain activity ought to be specified as indicators of effective drug action. In humans brain activity can be monitored mainly by EEG recording and by evoked potential registration. Systemic injection of acetylcholinesterase inhibitors induces EEG desynchronization in cats (Bradley and Elkes 1953; Rothballer et al. 1961) and rabbits (Longo and Silvestrini 1957). The experimental basis for a similar action of AChE inhibitors in humans is less convincing. Few systematic studies of the EEG effects of AChE inhibitors have been conducted. Most of those available (Grob et al. 1947; Rowntree et al. 1950; Lesny and Volja 1960; Goldstein and Beck 1965; Reiger and Okonek 1975; Sitaram et al. 1977; Pfefferbaum et al. 1979) have produced inconsistent results and are difficult to interpret due to differences in the drugs used, dosage range and EEG assessment techniques.

The parallelism between ACh action and the arousal effect, which has been demonstrated for the EEG, becomes less evident when sensory evoked potentials are studied. Their rhythmic afterdischarge, which is suppressed by natural and reticular arousal (Fleming and Evarts 1959) is markedly enhanced by physostigmine in the cat (Steriade 1968; Montplaisir and Sazie 1973). Analogue studies have not been performed in humans. In a search for ACh sensitive parameters of brain activity we studied the effect of the long acting cholinesterase inhibitor galanthamine (GAL) on the alpha power of the EEG and on the rhythmic afterdischarge of visual evoked potentials (VEPs).

Methods

Subjects

Recording of EEG and of flash VEP was performed in 8 male volunteers (A–H), aged from 20 to 35 years. Another subject (B.B.) was a 54-year-old volunteer, who exhibited extraordinarily stable late components of VEPs in a pre-experiment. In this subject only VEP studies were done. All subjects were non-obese (body weights 60–88 kg) and proven healthy in an initial medical examination including electrocardiogram,

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measurement of blood pressure and estimation of various laboratory parameters. None of the subjects smoked or had a known history of drug or alcohol abuse. Subjects were informed about the purpose of the study and gave their written consent.

GAL infusion and estimation of enzyme inhibition

Galanthamine hydrobromide 5 mg ampoules were diluted in saline 0.9% to produce a constant rate i.v. infusion. In 8 subjects (A–H) 10 mg GAL were applied over 30 min. In subjects A, E and G higher doses (35, 20 and 25 mg) were applied in a second experiment. In subject B.B. doses of 15 and 20 mg were used.

The catalytic activity of AChE in erythrocytes was measured as previously described in detail (Thomsen and Kewitz 1990) using [^{14}C]acetylcholine iodide (NEN, Dreieich, F.R.G.) radiolabelled in the acetyl moiety at final substrate concentrations of 3.6 mmol/l, at pH 7.4 and 25°C.

Timing of experiments

Subjects arrived at the hospital early in the morning in the fasting state and in-dwelling cannulae of FEP Teflon were applied to both arms separately for the infusion of GAL and collection of blood samples. Subjects entered the sound-proof electrically shielded EEG laboratory at 8.30 a.m.

Fig. 1 displays the timing of EEG and VEP recording in the experiments with infusion of 10 mg GAL over 30 min (8 experiments, subjects A–H). In the 3 experiments with higher doses in subjects A, E and G timing of VEP recording and of blood sampling during the infusion was varied slightly because of different infusion times but remained unchanged in the phases prior to and after infusion. In 3 experiments performed on subject B.B. a different timing of VEP recording was used, as indicated in Fig. 4. In one of these experiments, placebo was given after 1 week of a double blind oral administration of 45 mg GAL. In all experiments blood pressure and pulse were measured several times and subjects were asked for specific and non-specific adverse reactions.

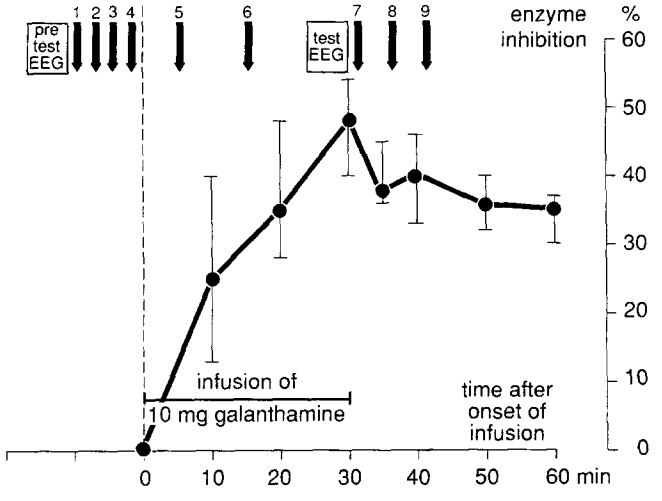

Fig. 1. Timing of experiments. 10 mg galanthamine were infused over 30 min. Several blood samples were taken for AChE activity. Black dots represent median enzyme inhibition in 8 subjects. Error bars indicate the first and third quartiles of data. Prior to infusion a pretest EEG and 4 flash VEPs (VEPs 1–4 as indicated by arrows) were recorded. Two VEPs (5 and 6) were recorded during infusion. The test EEG was recorded within the last 5 min of infusion and 3 VEPs (7–9) after the infusion.

EEG

Recording

A 16-channel electrodiagnostic system was used. Electrodes were applied to the scalp according to a modified international 10–20 system (no electrodes on the midline). Linked earlobes served as reference. Electrode impedances were maintained at less than 5 kΩ. The band width was 0.5–30 Hz. Signals were digitized at a sampling rate of 100/sec and stored on hard disc. Additionally the amplified and filtered analogue signals were recorded with a separate 16-channel polygraph.

The total duration of a recording was 5 min. During the first 2 min subjects were instructed to close the eyes and to minimize blinks and eye movements. For evaluation, data from the last 3 min were used.

Evaluation

The EEG was inspected for artifacts. Out of the artifact-free sequences ten 5 sec epochs were chosen randomly by the computer. Data from the 6 electrodes O_1, O_2, P_3, P_4, T_5 and T_6 were processed. In each epoch power spectra were computed for each of the 6 electrodes. From the resulting 6 spectra of an epoch one average spectrum S_{ae} was calculated. Averaging the 10 spectra S_{ae} from the 10 epochs yielded one average spectrum S_a. Pairs of power spectra S_a are displayed in Fig. 3.

Due to the length of the epochs (the exact value was 5.11 sec), the discrete frequencies in our spectra were multiples of $1/5.11 \approx 0.195$ Hz. Frequency bands were defined as delta (0.39–3.9 Hz), theta (4.1–7.8 Hz), alpha (8.0–12.9 Hz) and beta (13.1–30 Hz).

In the average spectrum S_a and in each of the 10 spectra S_{ae} 3 parameters were calculated for each frequency band: (1) the total power $P = \Sigma S(f)$ (f is the frequency, S(f) is the power spectrum; summation is performed within the band limits); (2) the mean frequency

$$f_m = \frac{\sum f \cdot S(f)}{\sum S(f)};$$

(3) the peak frequency f_p. Changes of P, f_m and f_p were used to quantify the effect of GAL infusion on the EEG. The differences ΔP, Δf_m and Δf_p in Table I were calculated from the parameters of the two spectra S_a of the pretest EEG and the test EEG. Significance of parameter change was tested with a t test, comparing the parameters from the 10 spectra S_{ae} of the pretest EEG with those of the test EEG.

Flash visual evoked potentials

The stimulus was a white Xenon flash (photostimulator strobotest LT 1001, Knott Elektronik, F.R.G.). With an intensity setting of II, an energy of 0.37 Joule/flash was obtained. Stimuli were applied binocularly with full-field stimulation. The distance between the lamp and the subject's eyes was 50 cm. Stimuli were presented with the eyes closed. Flash repetition rate was 1.5/sec. The evoked responses were recorded from right occipital electrode O_2 with midfrontal F_z as reference. Amplifier bandpass was 2–1000 Hz. Signals were digitized at 2000 samples/sec. Sampling period was 500 msec. Each averaged response consisted of 100 sweeps. Labelling of peaks and quantification of rhythmic afterdischarge by calculating the amplitude sum are shown in Fig. 2.

Results

(I) Effect of GAL on spontaneous EEG

All subjects had a dominant alpha rhythm and only small beta, theta and delta components. The delta portion of the spectrum, which is likely to contain artifacts, was not considered for evaluation. In the beta and theta band only power changes were taken into consideration because no stable frequency peaks could be found in most cases. Power spectra of pretest and test EEGs in the frequency range from 4 Hz to 18 Hz are displayed in Fig. 3; quantitative results are given in Table I.

Alpha power. After infusion of 10 mg GAL and a median erythrocyte esterase inhibition of 47% (Fig. 1) alpha power increased significantly in 4 of 8 subjects. The decrease of alpha power observed in the remaining 4 subjects was not significant. 10 mg GAL were tolerated without autonomic side effects. Increase of

TABLE I

Changes of EEG power spectra and of VEP rhythmic afterdischarge. Same denotation of subjects as used in Fig. 3; additional VEP data from subject B.B. are shown. Doses of galanthamine are presented in the second column. For significant changes of EEG and VEP parameters numerical values are given. Otherwise only the direction of change is indicated (+/0/−).

EEG. Power and frequency parameters are obtained from the pairs of average spectra displayed in Fig. 3 (average spectra from 6 electrodes O_1, O_2, P_3, P_4, T_5, T_6; averages of 10 epochs of 5 sec duration). To test significance of parameter changes we calculated the parameters for each 5 sec epoch separately and used a t test (10 epochs of pretest EEG versus 10 epochs of test EEG; $P = 0.05$). ΔP: change of power in the specified frequency band. Δf_p: change of peak frequency. Δf_m: change of mean frequency. f_p and f_m are estimated within the frequency limits of the alpha band. In subject A significance of Δf_p is tested separately for the lower frequency peak P_1 and for the second peak P_2. In subject H Δf_p is not specified (2 peaks in the pretest EEG but only 1 peak in the test EEG).

VEP. Amplitude sums AS of late VEP components were estimated as described in the legend of Fig. 2. In experiments on subjects A–H average amplitude sums of VEPs 7, 8 and 9 were compared with those of the pretest VEPs (t test: $P = 0.05$; for timing of experiments see Fig. 1). In subject B.B. timing of VEP recording was different, as labelled in Fig. 4. In these experiments average amplitude sums of the test VEPs were calculated from the last 2 records during infusion (infused doses 9.8 mg or more in Fig. 4A and C) and from the following 2 records after end of infusion.

Subject	Dose (mg)	EEG								VEP	
		Alpha (8.0–12.9 Hz)				Theta (4.1–7.8 Hz)		Beta (13.1–30 Hz)		Change of amplitude sums	
		ΔP (μV^2)		Δf_p (Hz)	Δf_m (Hz)	ΔP (μV^2)		ΔP (μV^2)		ΔAS (μV)	
A	10	+	23.4	− 0.59 (P_1) − 0.34 (P_2)	− 0.30	−		−		+	
B	10	+	7.8	−	0.00	−		−		+	8.7
C	10	−		0.00	0.00	+	3.37	+		+	8.7
D	10	−		− 0.39	− 0.32	−		−		+	
E	10	+	11.7	− 0.59	− 0.48	−		−		+	
F	10	−		− 0.98	− 0.53	−		−	2.40	+	
G	10	+	11.5	− 0.39	− 0.22	−		−		−	11.3
H	10	−			0.00	−		−		+	
A	35	+		− 0.98 (P_1) − 0.39 (P_2)	− 0.29	−	2.15	−	2.56	+	
E	20	+	19.7	− 0.98	− 0.77	−		−	0.87	+	
G	25	+		− 0.78	− 0.57	−		−		−	21.4
B.B.	15									+	22.5
B.B.	placebo									−	
B.B.	20									+	32.7

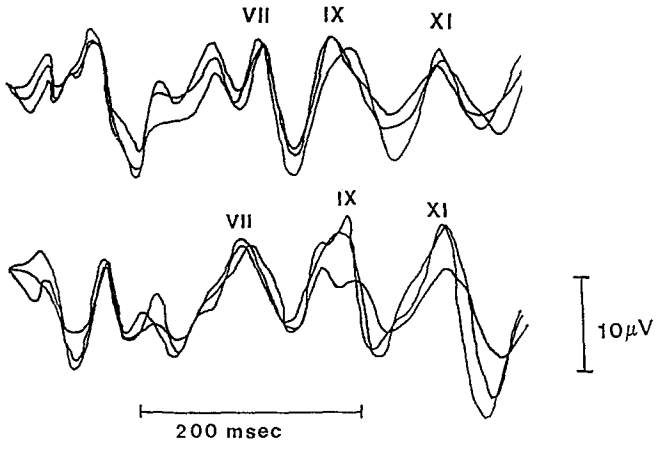

Fig. 2. Rhythmic afterdischarge of flash evoked visual potentials. Control responses of 2 subjects. Three averaged responses of 1 subject are superimposed on each trace. Wave VII, as defined by Cigánek (1961). The consecutive waves of the afterdischarge are accordingly labelled IX and XI. Peak-to-peak amplitudes of waves VII, IX and XI were measured from each negative peak to following positivity. Strength of afterdischarge is expressed as the sum of these amplitudes (AS). Mean and standard deviations of peak latencies (msec) of waves VII, IX and XI (control values from 9 subjects): VII: 235.2 ± 15.8; IX: 316.1 ± 24.6; XI: 402.6 ± 18.4.

the dose to 20–35 mg in subjects A, E and G caused a further increase of alpha power in 1 (E) and nausea and vomiting in 2 of the 3 subjects (A, E). Behavioural drug effects, such as changes of vigilance and of mental and emotional status were not observed by us or reported by the subjects on questioning.

Alpha frequency. After infusion of 10 mg GAL the mean frequency f_m and peak frequency f_p of the alpha rhythm decreased significantly by 0.22–0.98 Hz in 5 of 8 subjects tested (Table I). Increase of the dose to 20–35 mg caused a further decrease in all the 3 subjects tested.

The significant increases of alpha power and the decreases of alpha frequency were not associated with significant changes of theta power. The decrease of alpha frequency is therefore not the expression of a generalized slowing of brain activity, but reflects a specific action of GAL on the generator of the alpha rhythm.

As a consequence of an inverse relationship between amplitude and frequency of the alpha rhythm (Knott and Travis 1937), an increase of alpha power caused by an amplitude increase should be associated

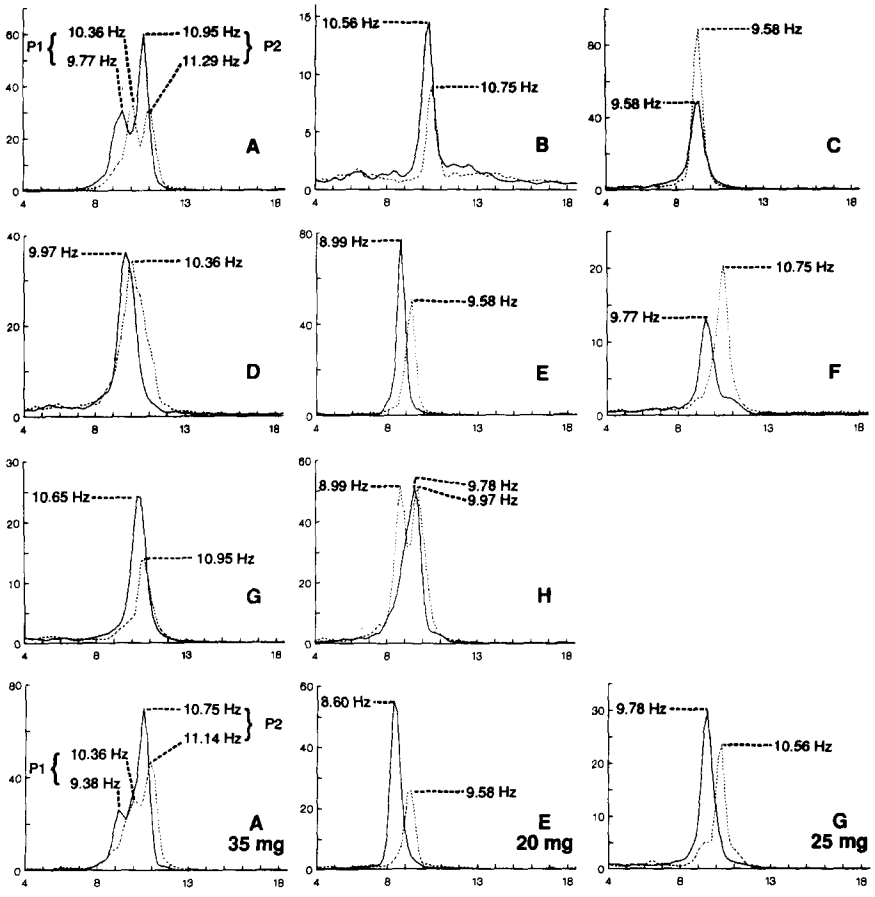

Fig. 3. EEG power spectra before (dotted lines) and after infusion of galanthamine (solid lines). Rows 1–3: infusion of 10 mg in 8 subjects (A–H). Bottom row: higher doses as indicated in subjects A, E and G. Power spectra of 50 sec of registration (average of 10 epochs of 5 sec) were calculated. The displayed curves represent the average of the spectra from the 6 posterior electrodes O_1, O_2, P_3, P_4, T_5 and T_6. Abscissa: frequency (Hz). Ordinate: spectral power density (μV^2/Hz). Note individual scaling of the ordinates.

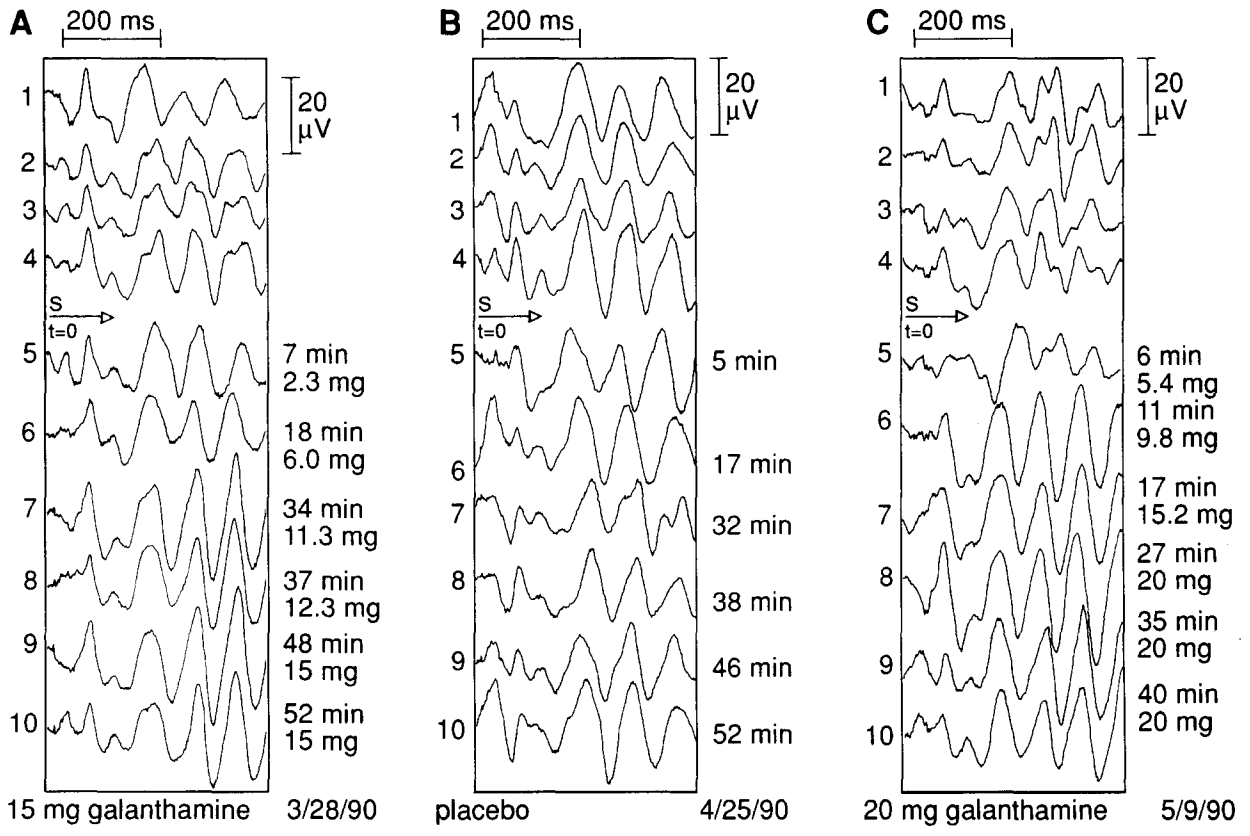

Fig. 4. Flash VEPs in subject B.B. Data from 3 experiments on different days. Consecutive records are shown from top to bottom. Arrows S indicate start of infusion. Traces 1–4: pretest VEPs. Traces 5–10: VEPs after start of infusion. Time elapsed after onset of infusion is labelled on the right of each curve. A, C: infusion of 15 mg galanthamine over 45 min (A) and of 20 mg over 22.5 min (C). The infused doses are labelled at each curve. Note onset of enhancement of afteroscillations in records corresponding to similar doses (11.3 mg in A; 9.8 mg in C). B: infusion of placebo over 45 min. Measurement after 1 week of oral administration of 45 mg galanthamine/day. The 4 pretest VEPs show larger amplitudes of rhythmic activity than the pretest VEPs in A and C but smaller amplitudes as compared with the curves in A and C near the end of infusion. No additional enhancement of rhythmic activity is seen in B under infusion of placebo.

with a decrease of frequency. The association of decreasing power with decreasing frequency, as observed in subjects D and F (Table I), suggests that the decrease of alpha frequency may be an independent effect.

The changes of alpha power or of alpha frequency were not significantly correlated with the inhibition of erythrocyte cholinesterase (Spearman rank correlation: $P = 0.05$).

(II) Action of GAL on flash VEP

Amplitude and latency of the flash P_2 component (P IV of Fig. 2) were not significantly affected by a dose of 10–35 mg GAL. In the majority of subjects there was a tendency towards a latency increase and an amplitude decrease after GAL. In 7 of 8 subjects receiving a total dose of 10 mg GAL, the amplitude sums of the rhythmic afterdischarge increased by 12–109% (Table I). However, this increase reached significance in only 2 subjects as a consequence of considerable variance of single response amplitudes.

Moreover, the amplitude sum decreased significantly in 1 subject (G). In the 3 subjects tested with doses of 20–35 mg (A, E, G) the amplitude sum increased or decreased further (Table I).

In subject B.B. 15 or 20 mg GAL induced significant enhancement, while placebo had no effect (Fig. 4 and Table I). The placebo was given after 1 week of a double blind oral administration of 45 mg GAL. As a consequence of this pretreatment the control values of the amplitude sums before infusion were significantly higher in this case (Fig. 4B) in comparison with experiments without pretreatment (Fig. 4A and C) but lower as compared with the curves in 4A and 4C near the end of infusion. The increase of the amplitude sum of the afterdischarge was significantly correlated with the strength of inhibition of erythrocyte acetylcholinesterase (Fig. 5; Spearman rank correlation coefficient: $r = 0.65$; $P = 0.05$).

Table I shows that changes of the afterdischarge were not necessarily associated with similar changes of the spontaneous alpha rhythm. In subject G, for in-

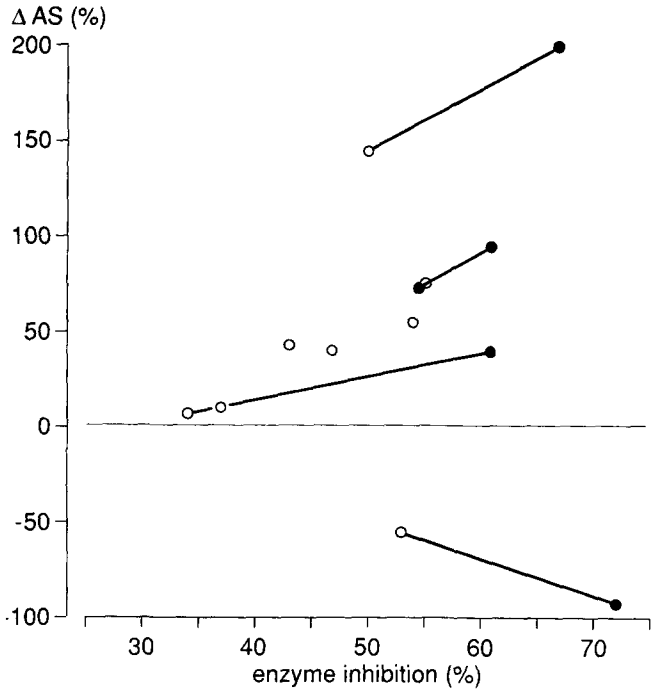

Fig. 5. Change of rhythmic afterdischarge of flash VEPs in dependence of inhibition of AChE in red blood cells. In each experiment the value of enzyme inhibition is taken from the blood sample at the end of infusion. Amplitude sum AS was estimated from the first VEP after end of infusion (VEP 7 in the 10 mg experiments, see Fig. 1). AS was calculated as demonstrated in Fig. 2. Percentual changes of AS in comparison with the pretest VEPs were used. Open circles: infusion of 10 mg galanthamine (N = 8). Dots: experiments with higher doses (N = 5). Straight lines connect values from the same subject.

stance, a significant increase of alpha power corresponded to a likewise significant decrease of the afterdischarge. This suggests that rhythmic afterdischarge and spontaneous alpha rhythms are generated by different neural oscillators.

Discussion

The synchronizing effect of AChE inhibition reported in this study contrasts with the result of animal experiments, which demonstrated desynchronizing effects of physostigmine (Bradley and Elkes 1953; Longo and Silvestrini 1957; Rothballer et al. 1961; Karczmar 1977). There are many indications that ACh mediates EEG desynchronization in activated brain states. Cortical release of ACh is increased during arousal and EEG desynchronization following rostral reticular and sensory stimulation (Celesia and Jasper 1966; Szerb 1967; Phillis 1968; Jasper and Koyama 1969). In the desynchronized brain states of natural wakefulness and REM sleep the rate of liberation of ACh increases in cats (Jasper and Tessier 1971). Also inconsistent with the data presented here are reports of increased fast activity or EEG desynchronization after cholinomimetics in humans (Grob et al. 1947; Pfeiffer et al. 1963; Goldstein and Beck 1965). Physostigmine infusion caused a time-dependent induction of REM sleep and arousal during normal human sleep, transforming synchronized brain states into desynchronized ones (Sitaram et al. 1977). The only comparable study on humans, which assessed the EEG effects of physostigmine by computerized EEG spectral analysis, reported an increase of alpha power after 0.5 mg physostigmine (Pfefferbaum et al. 1979). Higher doses of physostigmine (1.25 mg, 2.5 mg) had no effect on the alpha power but resulted in a decrease of peak and mean alpha frequency with a concomitant increase in the amount of slow activity (delta and theta). The decrease of alpha frequency was therefore interpreted as a component of a generalized, possibly unspecific, slowing of brain activity (Pfefferbaum et al. 1979). In our experiments the decrease of peak and mean alpha frequency was dose related but not associated with toxic side effects and without a concomitant increase of theta and delta power. It is therefore not the expression of a generalized slowing of brain activity, but reflects a specific action of GAL on the generator mechanism of the alpha rhythm.

Our results are also supported by the findings of Itil and Fink (1968), who demonstrated a considerable decrease of human alpha activity with and without increase of slow frequency components after low doses of the anticholinergic drugs ditran and atropine. The alpha decrease by substances with antimuscarinic action suggests that the increase of alpha power after AChE inhibition is a muscarinic effect.

The discrepancy between the physostigmine-induced EEG desynchronization in animals and the results of human studies may be resolved by realizing that synchronized rhythms in states of lowered vigilance, such as spindles, were predominantly blocked by cholinomimetic drugs. Spindle rhythmicity and synchronization depend on periodic pacemaker activity of the n. reticularis thalami (Steriade et al. 1985, 1987), which provides cyclic inhibition of lateral thalamic relay neurones, and on the Ca^{2+}-dependent rebound activation of lateral thalamic relay cells, which follows cyclic inhibition (Deschênes et al. 1984). Rhythmic pacemaker activity of the n. reticularis is suppressed and spindle oscillations are blocked by brain-stem cholinergic afferents (Hu et al. 1989). The alpha rhythm, a correlate of the waking state, differs in some essential properties from spindling and may depend on other mechanisms than spindles, which were regarded as an animal analogue of human alpha activity (Andersen and Andersson 1968). It is true that alpha activity, like spindling, is blocked by arousing stimuli, but it is enhanced in some tasks requiring increased attention (Creutzfeldt et al. 1969; Ray and Cole 1985). Further-

more, thalamo-cortical and cortico-cortical systems seem to interact in the generation and synchronization of cortical alpha rhythms (Lopes da Silva et al. 1973; Steriade et al. 1990), while cortical spindle rhythmicity and spindle synchronization depend essentially on rhythmic thalamo-cortical input.

In the majority of our subjects the amplitude of the flash evoked rhythmic afterdischarge increased dose-related after GAL. P_2, the early component of the flash evoked response, which was reported to be delayed by the anticholinergic drug hyoscine (Bajalan et al. 1986), remained unaffected. Changes of the afterdischarge were not necessarily associated with similar changes of the spontaneous alpha rhythm. This suggests that the rhythmic afterdischarge and the spontaneous alpha rhythm are generated by different neural oscillators. Our findings are in agreement with results of animal experiments, which demonstrated enhancement of the rhythmic afterdischarge of visual or acoustic cortex of the cat after intravenous injection of eserine (Steriade 1968; Montplaisir and Sazie 1973) and suppression of afterdischarges by scopolamine (Montplaisir and Sazie 1973) or after intravenous and cortical application of atropine (Szerb 1965). Krnjević and Phillis (1963) have reported that in the depth of somatosensory cortex cholinoceptive cells respond to sensory stimulation by repetitive bursts at a rate of rhythmic afterdischarge. The afterdischarge-like repetitive discharges of single units were abolished by microiontophoretic application of atropine. These results indicate that the cortical rhythmic afterdischarge after sensory stimulation depends on cholinergic cortical synapses. In our case, a cortical site of action of GAL on the visual evoked afterdischarge seems therefore probable.

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