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Central effects of the angiotensin-converting enzyme inhibitor, captopril
II. Electroencephalogram and body sway

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1 Effects of single doses of captopril (12.5, 25 and 50 mg) on the electroencephalogram (EEG) and on body sway were studied in fourteen healthy male subjects. Oxazepam (15 mg), as an active control, and two placebos were included in the study, together with a single dose of atenolol (100 mg). Medication was administered double-blind at 11.00 h, and assessments made before and at 2 and 4 h after drug ingestion.

2 There were no changes in the EEG with captopril. Oxazepam reduced the circadian rise in alpha activity, while atenolol decreased beta power. Delta activity was modified by both oxazepam and atenolol.

3 A reduction in lower frequencies of body sway (0.05–1 Hz) occurred with captopril, while the spectra were unaffected by oxazepam. Atenolol increased ($P < 0.05$) activity in the frequency range 0.75–2.75 Hz.

4 These observations suggest that captopril is free of central effects such as sedation that may occur with β-adrenoceptor antagonists. Reduced body sway with captopril could reflect improved integration of central and peripheral control of posture.

Keywords captopril electroencephalogram body sway

Introduction

Previous studies with the electroencephalogram (Nicholson *et al.*, 1988) have shown that β-adrenoceptor antagonists modify the electrical activity of the central nervous system. The changes are subjectively appreciated as sedation and reduced alertness, which is a common side effect of many antihypertensive drugs (Croog *et al.*, 1986). However, the angiotensin-converting enzyme inhibitor, captopril, has been reported to enhance work-related performance relative to other hypotensive medication (Croog *et al.*, 1986). Nevertheless, the potential effect of this drug on the central nervous function in man *per se* has received little attention, and the present study extends our assessment of the central effects of antihypertensive drugs to an ACE inhibitor by examining its potential effects on body sway and on the electrical activity of the brain.

Methods

Experimental design

Details of the design and methodology relating to performance tests and subjective assessments are described in Part I of the study (Currie *et al.*, 1990). The study was designed to assess possible central effects of captopril, and as a dose-response study. A single dose of atenolol was included to

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corroborate our previous findings (Nicholson *et al.*, 1988). The drugs were ingested orally at 11.00 h, and recordings of the EEG and body sway were made before drug ingestion (10.00 h) and at 2 (13.00 h) and 4 (15.00 h) h thereafter.

Electroencephalograms

Resting activity was recorded from P3-01, P4-02 and C3-T3 (10–20 international system), using silver-silver chloride electrodes with inter-electrode resistances less than 10 kΩ. The EEG was recorded for 2 min with eyes open while the subjects performed a mental arithmetic task, and this was followed by a 5 min recording with the eyes closed, during which time the subjects were instructed to relax. The signals were recorded on magnetic cassettes (TDK 60) using ambulatory four-channel Medilog recorders (Oxford Medilog Systems, Model 4-24).

The tapes were replayed at 20 times real-time using a Medilog Page Mode Display (PMD-12) controlled by a PDP11-34 computer. The analogue data were low pass filtered before digitisation at a sampling rate of 2560 Hz (equivalent to 128 Hz real-time). Epochs containing artefacts were identified and excluded from subsequent analysis. From each recording with eyes open, fifteen epochs of 4 s duration were analysed, and power spectra (0.25 Hz resolution) for each epoch were computed using a fast Fourier transform. A mean power spectrum based on fifteen epochs (1 min of data) was then calculated. Sixty epochs of 4 s were analysed from each recording with eyes closed, and four mean power spectra (0.25 Hz resolution) relating to consecutive intervals of 1 min calculated. From each mean spectrum (one eyes open, four eyes closed), the total power in six bands (delta: 0.5–3 Hz, theta: 3.5–7.0 Hz, alpha 1: 7.5–10 Hz, alpha 2: 10.5–13 Hz, beta 1: 13.5–21 Hz, beta 2: 21.5–30 Hz) were computed.

Body sway

The subjects stood on a rigid platform which rested on three pressure transducers (one at the front, two at the back), providing measurement of lateral and anterior body sway. Data were recorded for 1 min with eyes open and then with eyes closed. For each recording, a period of 32 s was digitised off-line at a sampling rate of 32 Hz. A mean power spectrum with resolution of 0.25 Hz over the frequency range 0.05 to 4 Hz was computed using a fast Fourier transform. Spectra from lateral and posterior channels were summed to give a single mean spectrum for each condition.

Statistical analysis

The methods of analysis are given in Part I of the study with the following differences. In the case of EEG data with eyes closed, a fourth factor (minutes) was included in the ANOVA model. For all EEG data, a logarithmic transform was applied to the power spectra, and drug effects were then estimated by calculating the difference between pre- and post-ingestion means to allow for day-to-day differences between pre-ingestion means. These differences were used to compare drug responses with the placebo value at each post-ingestion time.

In the case of body sway, principal components analysis was applied to the spectra, resulting in orthogonal vectors representing the data. Direct comparisons of component weights were then made between drug and placebo conditions at post-ingestion times.

Results

Electroencephalograms

Detailed results of the effects of captopril and atenolol are shown in Figure 1, with changes in EEG activity presented on a logarithmic scale. A summary of the findings is given below.

Recordings with eyes open The placebo demonstrated an increase in activity from pre-ingestion time to 2 and 4 h after ingestion. Oxazepam reduced alpha 1 and alpha 2 power in channel P3-01, increased beta 1 in P4-02 and reduced delta, alpha 1, alpha 2 and beta 2 activity in C3-T3. Atenolol reduced delta and theta power in P3-01 and delta, beta 1 and beta 2 power in C3-T3. No changes in the EEG were seen with captopril.

Recordings with eyes closed Activity of the EEG with placebo was increased at 2 and 4 h after ingestion compared with pre-ingestion levels. Oxazepam reduced alpha 1 and alpha 2, and increased delta power in all channels. No changes in activity of the EEG were evident with either atenolol or captopril.

Body sway

The power spectra of body sway amplitudes with eyes open and with eyes closed were analysed separately, using principal components analysis. The spectra with eyes open were represented by three components, covering the frequency ranges 0.05–1 Hz, 0.75–2.75 Hz and 1.75–4 Hz respectively, while with eyes closed, two components

Table 1 Effects of captopril and atenolol on body sway with eyes open (means for 14 subjects). Values are weights on principal components

	Time after ingestion (h)	*Placebo*	*Oxazepam 15 mg*	*Atenolol 100 mg*	*Captopril*				
					12.5 mg	*25 mg*	*50 mg*	*Mean for 12.5–50 mg*	*Standard error†*
0.05–1 Hz	2	0.267	0.368	0.108	0.085	–0.011	–0.268*	–0.065*	0.160
	4	0.176	0.090	0.031	–0.064	0.061	–0.184	–0.062	
	Mean 2, 4	0.221	0.228	0.069	0.011	0.025	–0.226*	–0.063*	0.128
0.75–2.75 Hz	2	–0.089	–0.440	0.476	–0.188	–0.400	–0.083	–0.224	0.212
	4	–0.034	–0.404	0.236	–0.177	–0.321	–0.073	–0.190	
	Mean 2, 4	–0.062	–0.422	0.356*	–0.183	–0.360	–0.078	–0.207	0.154
1.75–4 Hz	2	–0.006	–0.017	0.063	–0.115	0.080	–0.148	–0.061	0.204
	4	0.106	–0.093	–0.027	–0.210	0.181	0.254	0.075	
	Mean 2, 4	0.050	–0.055	0.018	–0.162	0.131	0.053	0.007	0.156

Significance levels: $*P < 0.05$
†Standard errors are pooled estimates taken from the analysis of variance table.

Table 2 Effects of captopril and atenolol on body sway with eyes closed (means for 14 subjects). Values are weights on principal components

	Time after ingestion (h)	*Placebo*	*Oxazepam 15 mg*	*Atenolol 100 mg*	*Captopril*				
					12.5 mg	*25 mg*	*50 mg*	*Mean for 12.5–50 mg*	*Standard error†*
0.05–1.5 Hz	2	0.163	0.157	0.018	0.111	0.021	–0.217	–0.028	0.166
	4	0.002	–0.066	0.277	–0.095	–0.190	–0.292	–0.192	
	Mean 2, 4	0.083	0.045	0.147	0.008	–0.084	–0.254*	–0.110	0.125
1.25–4 Hz	2	–0.175	–0.502	0.304	–0.278	–0.115	0.131	–0.087	0.230
	4	–0.046	–0.222	–0.237	–0.151	0.095	–0.268	–0.108	
	Mean 2, 4	–0.111	–0.362	0.034	–0.215	–0.010	–0.069	–0.098	0.176

Significance levels: $*P < 0.10$
†Standard errors are pooled estimates taken from the analysis of variance table.

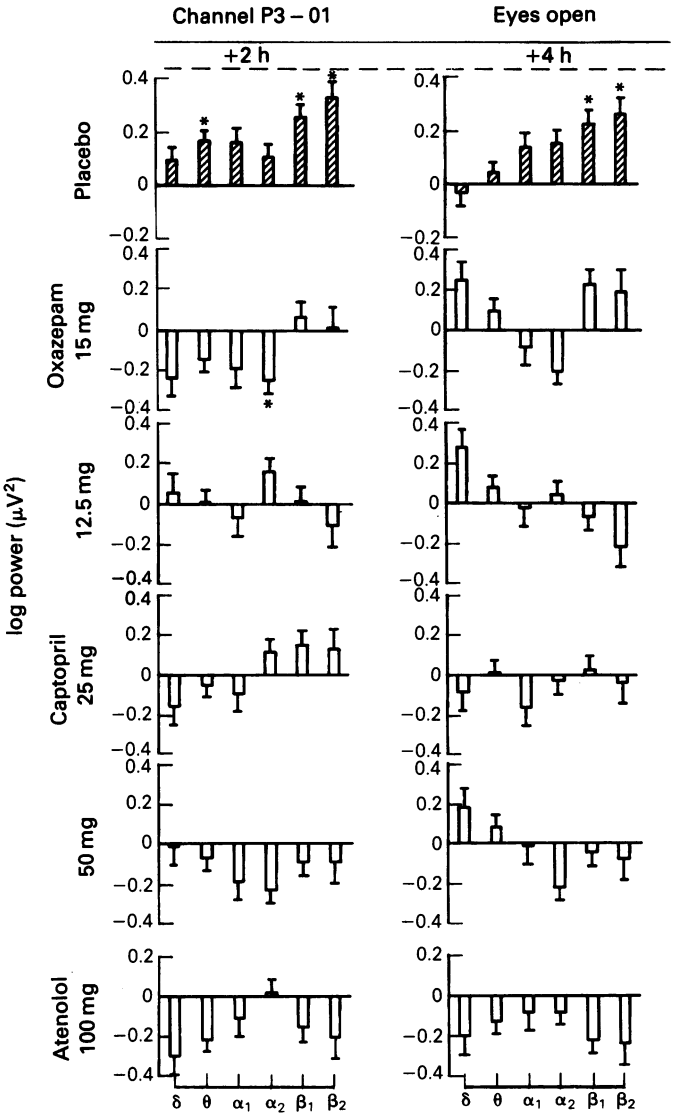
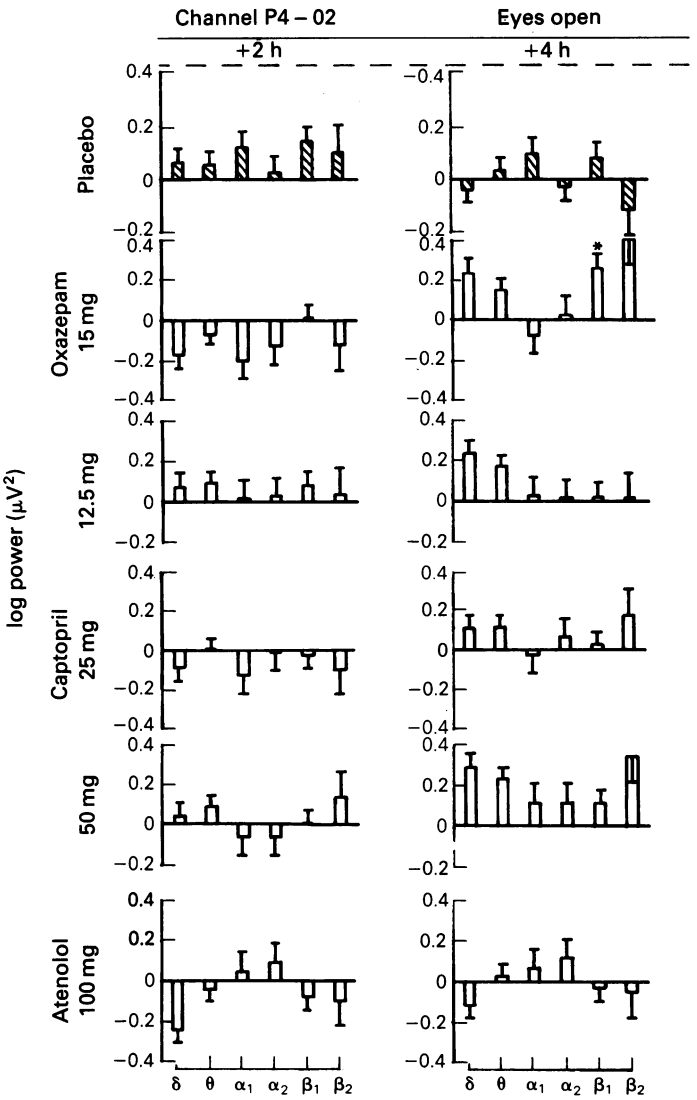


Figure 1 Effects of captopril and atenolol on the EEG at 2 and 4 h after ingestion. The EEG variables are define as δ: 0.5–3 Hz; θ: 3.5–7 Hz; α_1: 7.5–10 Hz; α_2: 10.5–13 Hz; β_1: 13.5–21 Hz; β_2: 21.5–30 Hz.

□ Indicates change at 2 and 4 h from pre-ingestion value with placebo. ■ Indicates the effect of each drug compared with placebo in the following manner: at 2 and 4 h after ingestion, the differences from pre-ingestion means were calculated, and these differences then subtracted from the change in placebo means from pre-ingestion to each post-ingestion time.

Differences are based on mean values for 14 subjects. Significance levels: $*P < 0.05$; $**P < 0.01$; $***P < 0.001$. The error bars represent pooled estimates of standard error taken from the analysis of variance.



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were identified, representing frequencies of 0.05–1.5 Hz and 1.25–4 Hz.

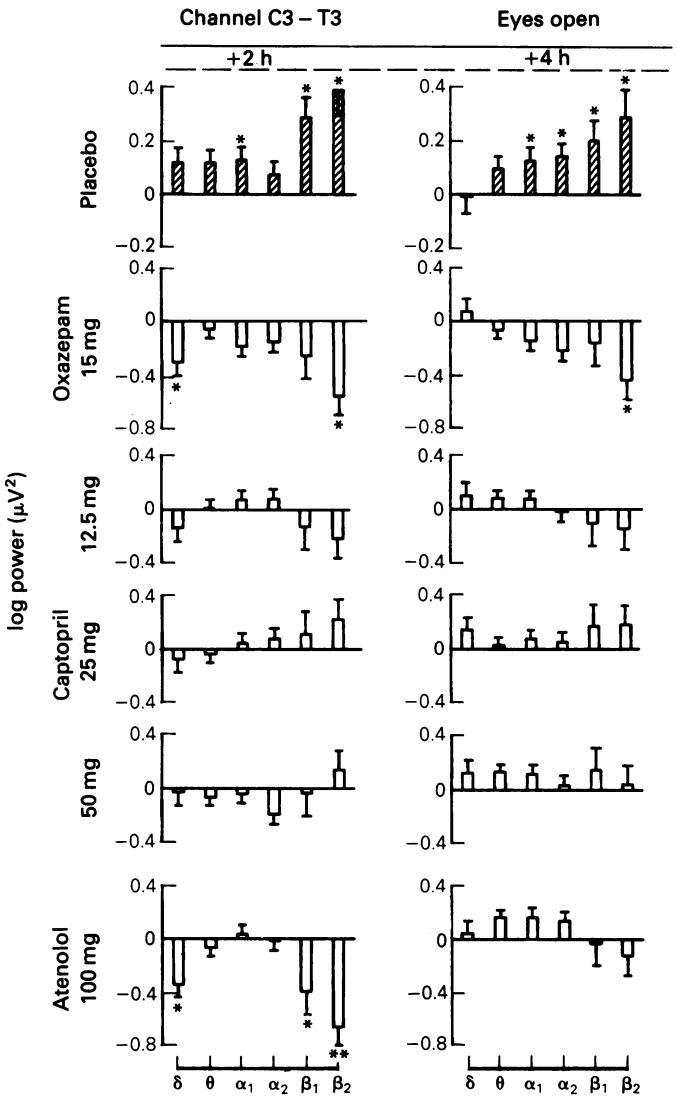
The results are shown in Tables 1 and 2.

Captopril reduced amplitude of lower frequency activity (0.05–1 Hz), the result being evident at the dose of 50 mg and when meaned over doses ($P < 0.05$). Body sway with eyes open was unaffected by oxazepam, while atenolol increased activity of the 0.75–2.75 Hz component ($P < 0.05$).

Recordings with eyes closed were unaffected by all drugs, although there was a tendency ($P <$ 0.10) for captopril (50 mg) to decrease low frequency activity (0.05–1.5 Hz).

Discussion

The present study has been unable to demonstrate changes in the electroencephalogram with captopril in the dose range 12.5–50 mg despite the known sensitivity of the EEG to the central effects of drugs (Saletu *et al.*, 1982; Sittig *et al.*, 1982). Although changes in the EEG with placebo



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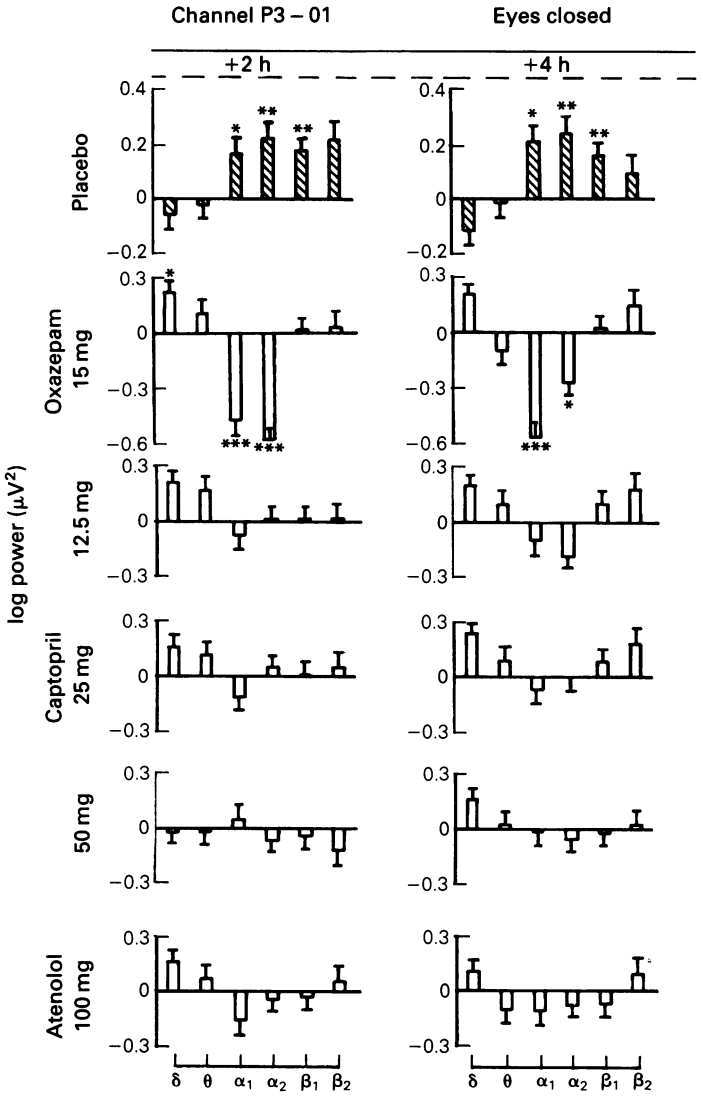
throughout the day occurred, and are likely to reflect the rising phase of alertness associated with the circadian rhythm (Nicholson *et al.*, 1989; Spencer, 1987), no reduction or reversal of this could be seen with any dose of captopril, in contrast with the changes in alpha and beta activity with oxazepam. The absence of change with captopril suggests that neither sedation nor improved alertness would occur and, although we did not observe enhanced subjective feelings of well-being, such changes have been seen in patients with captopril when compared with other antihypertensive drugs (Croog *et al.*, 1986). Similar studies with enalapril (Frcka & Lader, 1988; Olajide & Lader, 1985) have also been unable to establish changes in the EEG. The absence of unequivocal changes in subjective feelings of alertness with captopril or with enalapril, therefore, support the lack of objective findings.

However, captopril may improve short-term memory (Currie *et al.*, 1990), and this would imply an effect of central origin. This does not seem to involve altered arousal as there were no changes in the EEG, subjective alertness or in attention-related tasks, but it could imply a



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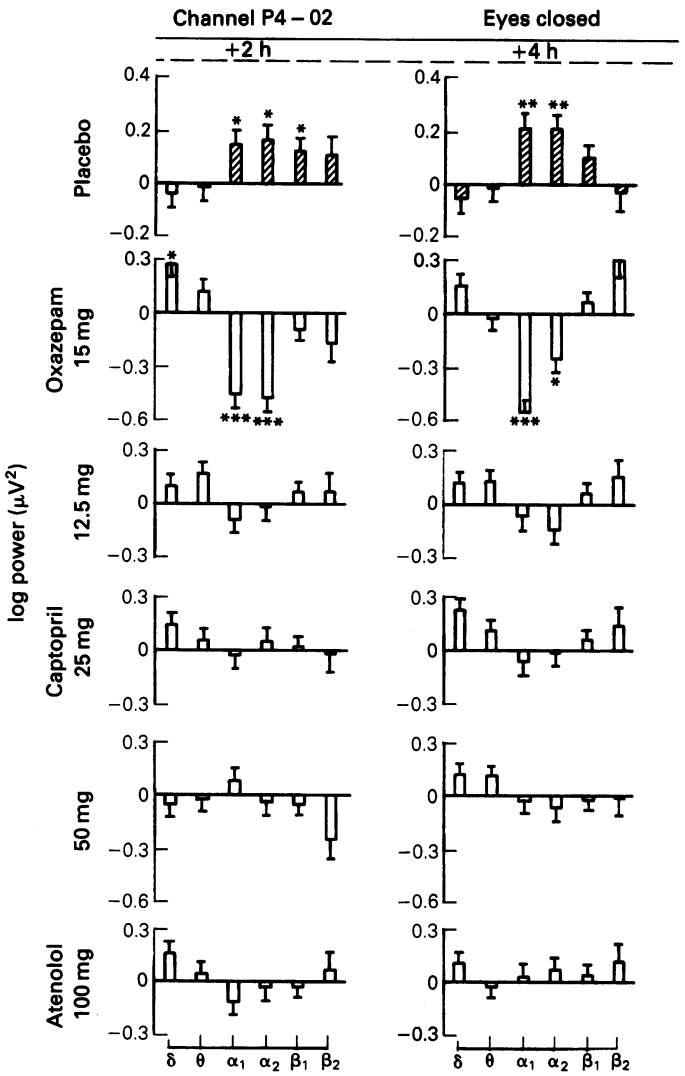
specific effect on memory processes. Though correlations of a central change of this nature may be made with event related potentials (Kunkel, 1988), the absence of change in the spontaneous activity of the brain would not appear to be at variance with the existence of a central effect.

Body sway was modified by captopril, with a reduction in amplitude of frequencies below 1.0 Hz occurring in recordings with eyes open. The maintenance of stable posture involves complex integration of central and peripheral nervous function, with low frequencies (less than 0.5 Hz) reflecting movement of the centre of gravity governed by the vestibular system, and oscillations of higher frequency arising from fine adjustments of muscular origin (Gurfinkel, 1973). Frequencies of approximately 1 Hz involve feedback from visual cues to the sensory-motor and vestibular systems. In this way captopril may improve central integration.

Body sway is a sensitive indicator of psychoactive drugs (McClelland, 1989), and in healthy volunteers increased amplitude is seen with both sedative (Matilla *et al.*, 1984; Nicholson *et al.*, 1988; Patat & Foulhoux, 1985) and stimulant (Franks *et al.*, 1975) compounds. In this sense, the reduction in amplitude with captopril sug-



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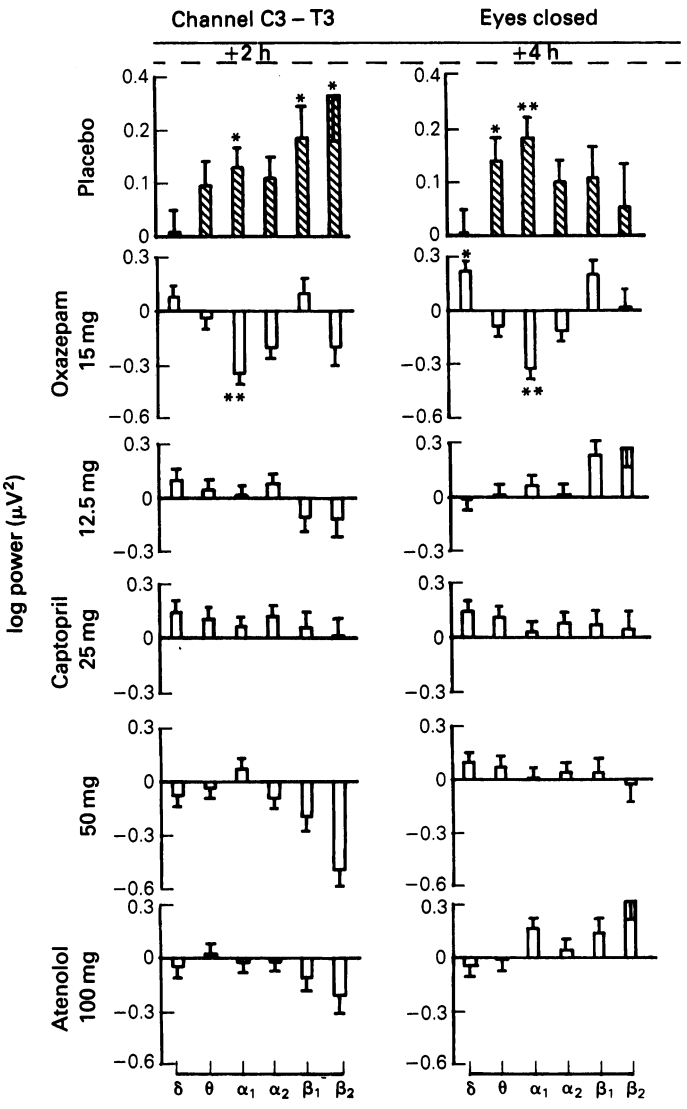
gests that changes with this drug are unlikely to be related to sedation or increased arousal. Decreases in body sway are not frequently observed, although the 'cerebral activator' vinpocetine is reported to reduce body sway in the elderly (Patat *et al.*, 1985), and this would imply that drugs can improve postural control when it is sub-optimal.

However, many stimulant drugs, while improving central function, adversely affect the peripheral nervous system and may therefore disrupt integration of the mechanisms which control body sway. No such adverse effects were seen with captopril, and, indeed, tasks involving motor function, such as finger-tapping, symbol copying and letter cancellation (Currie *et al.*, 1990; Frcka & Lader, 1988; Olajide & Lader, 1985) improved. Although reduction in body sway may reflect subtle changes in the reactivity of the brain stem, a more peripheral effect on posture would be consistent with the findings with tasks involving a motor component.

Finally, our findings with atenolol imply the likelihood of central effects occurring with this drug, as indicated by the changes in the EEG, and are in general agreement with our previous result (Nicholson *et al.*, 1988). The change in amplitude of body sway, with higher frequencies



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increasing, may indicate the likelihood of a peripheral effect with this drug.

In conclusion, we have been unable to demonstrate any changes in the spontaneous electrical activity of the brain with captopril, and this would suggest that it is free of central effects such as sedation and reduced alertness which are associated with other antihypertensive drugs including β-adrenoceptor antagonists and methyldopa. These findings are consistent with the absence of change in subjectively assessed alertness (Currie *et al.*, 1990). However, although no adverse effects could be established, improved memory performance suggests that changes in the central nervous system occur, while reduced body sway may reflect improved integration of central and peripheral control of posture.

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References

Croog, S. H., Levine, S., Testa, M. A., Brown, B., Bulpitt, C. J., Jenkins, C. D., Klerman, G. L. & Williams, G. H. (1986). The effects of antihypertensive therapy on quality of life. *New Engl. J. Med.*, **314**, 1657–1664.

Currie, D., Lewis, R., McDevitt, D. G., Nicholson, A. N. & Wright, N. A. (1990). Central effects of the angiotensin-converting enzyme inhibitor, captopril I—Performance and subjective assessment of mood. *Br. J. clin. Pharmac.*, **30**, 527–535.

Franks, H. M., Hagedorn, H., Hensley, V. R., Hensley, W. J. & Starmer, G. A. (1975). The effect of caffeine on human performance, alone and in combination with ethanol. *Psychopharmacologia*, **45**, 177–181.

Frcka, G. & Lader, M. (1988). Psychotropic effects of repeated doses of enalapril, propranolol and atenolol in normal subjects. *Br. J. clin. Pharmac.*, **25**, 67–73.

Gurfinkel, E. V. (1973). Physical foundations of stabilometry. *Agressologie*, **14**, C9–14.

Kunkel, H. (1988). *On the use of event-related potentials in pharmaco-EEG.* International Pharmaco-EEG Symposium, Kobe, Japan. Nov, 1988.

Matilla, M. J., Aranko, K., Matilla, M. E. & Stromberg, C. (1984). Objective and subjective assessments of hangover during subacute administration of temazepam and nitrazepam to healthy subjects. *Eur. J. clin. Pharmac.*, **26**, 355–380.

McClelland, G. R. (1989). Body sway and the effects of psychoactive drugs—a review. *Human Psychopharmacology*, **4**, (in press).

Nicholson, A. N., Stone, B. M., Wright, N. A. & Belyavin, A. J. (1989). Daytime sleep latencies: relationships with the electroencephalogram and with performance. *J. Psychophysiology*, **3**, 387–395.

Nicholson, A. N., Wright, N. A., Zetlein, M. B., Currie, D. & McDevitt, D. G. (1988). Central effects of β-adrenoceptor antagonists II—Electroencephalogram and body sway. *Br. J. clin. Pharmac.*, **26**, 129–141.

Olajide, D. & Lader, M. (1985). Psychotropic effects of enalapril maleate in normal volunteers. *Psychopharmacology*, **86**, 374–376.

Patat, A. & Foulhoux, P. (1985). Effect on postural sway of various benzodiazepine tranquillizers. *Br. J. clin. Pharmac.*, **20**, 9–16.

Patat, A., Le Go, A. & Foulhoux, P. (1985). Dose-response relationship of vindeburnol based on spectral analysis of posturographic recordings. *Eur. J. clin. Pharmac.*, **29**, 455–459.

Saletu, B., Grunberger, J., Taeuber, K. & Nitsche, V. (1982). Relation between pharmacodynamics and -kinetics: EEG and psychometric studies with cinolazepam and nomifensine. In *Electroencephalography in drug research*, ed. Herrmann, W. M., pp. 89–111. New York: Gustav Fischer.

Sittig, W., Badian, M., Rupp, W. & Taeuber, K. (1982). Performance tests and pharmaco-EEG after 1,4 and 1,5 benzodiazepines. In *Electroencephalography in drug research*, ed. Herrmann, W. M., pp. 113–129. New York: Gustav Fischer.

Spencer, M. B. (1987). The influence of irregularity of rest and activity on performance: a model based on time since sleep and time of day. *Ergonomics*, **30**, 1275–1286.

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