Low plasma concentrations of adrenaline and physiological tremor in man

IW FELLOWS, IA MACDONALD, HJ WHARRAD, AT BIRMINGHAM

From the Department of Physiology and Pharmacology, Queen's Medical Centre, Nottingham, UK

SUMMARY Finger tremor was measured in six normal subjects during intravenous infusions of adrenaline ($10 \text{ ng kg}^{-1} \text{ min}^{-1}$ and $50 \text{ ng kg}^{-1} \text{ min}^{-1}$) resulting in venous plasma adrenaline concentrations within the physiological range (0.77 ± 0.08 and $2.28 \pm 0.18 \text{ nmol l}^{-1}$). Tremor amplitude significantly increased after 15 and 25 minutes infusion at the higher dose of adrenaline. The lower dose of adrenaline increased tremor in three of the six subjects.

Adrenaline infused intravenously increased the amplitude of tremor in patients with Parkinson's disease.¹⁻⁴ Marsden *et al* showed that a similar effect was seen when adrenaline was infused intravenously into normal subjects and they demonstrated that the receptors responsible for the increase in tremor were in the forearm.⁵

With the advent of newly-developed methods for the measurement of catecholamines it has become clear that the doses of adrenaline used in earlier studies would have resulted in plasma adrenaline concentrations much higher than those likely to be encountered in physiological situations. The present study was designed to determine whether or not rates of infusion of adrenaline resulting in plasma adrenaline concentrations within the physiological range produced measurable increases in finger tremor.

Methods

Six healthy males (aged 20-30 years, all right-handed) gave informed consent to participate in the study which was approved by the Medical School Ethical Committee. The subjects were studied supine in a constant temperature room at 30°C ; they had not taken alcohol or caffeine-containing beverages for at least 16 hours before the tremor measurement and had only consumed a light breakfast before 08.00 hours. One of the subjects was a smoker but did not smoke on the day of the tests. Each subject sat in the laboratory for 30 minutes before the experiment. Venous cannulae were inserted, one into a vein in the right forearm and another in the left forearm, and the subject then rested

supine for 30 minutes. Solutions were infused into the superficial right forearm vein over 30 minutes and venous blood samples were obtained from the indwelling left antecubital venous cannula. The plasma was assayed for adrenaline and noradrenaline concentration.⁶ Tremor was measured for 1 minute periods before, and at 5, 15 and 25 minutes during each 30 minute infusion and again at 10 and 20 minutes after each infusion.

On three separate occasions at least one week apart at the same time of day (always in the afternoon) the subjects received (1) adrenaline $50 \text{ ng kg}^{-1} \text{ min}^{-1}$ diluted in saline ($154 \text{ mmol NaCl l}^{-1}$) containing ascorbic acid (1 mg ml^{-1}) (referred to as adrenaline-50) or (2) adrenaline $10 \text{ ng kg}^{-1} \text{ min}^{-1}$ in the same diluent (referred to as adrenaline-10) or (3) saline ($154 \text{ mmol NaCl l}^{-1}$) containing ascorbic acid (1 mg ml^{-1}) (control).

Tremor measurement

Measurements of finger tremor of the right hand were made using a small accelerometer (mass 13 g) (Bruel and Kjaer type 4367) attached by a "Perspex" ring (mass 2 g) to the terminal phalanx of the middle finger.⁷ Recordings were made with the forearm supported and the hand outstretched. All measurements were made with the subjects supine. Measurements were made for one minute and recorded via a charge amplifier (Bruel and Kjaer type 2635) onto a Racal FM taperecorder for further analysis.

Tremor analysis

Frequency analysis of the tremor waveform, filtered to remove frequencies above 50 Hz to prevent alias contamination, was carried out using a Hewlett-Packard 3582A spectrum analyser, remotely programmed with a type 9825A desk-top calculator in conjunction with a type 7225A graph plotter and double disc drive (HP 9885S and HP 9885M). Five second epochs of the analogue signal were digitised and subjected to Fourier analysis; the frequency spectra from eight sequential epochs were averaged to yield for each subject a mean frequency spectrum covering the range 0.4 to 51.2 Hz in 0.2 Hz intervals. A Hann passband was used to minimise leakage. From the frequency spectrum the root

Address for reprint requests: Professor AT Birmingham, Department of Physiology and Pharmacology, Medical School, Queen's Medical Centre, Nottingham NG7 2UH, UK.

Received 25 June 1985

Accepted 23 July 1985

mean square (rms) of tremor amplitude was calculated for the 0–50 Hz and the 8–11 Hz frequency bands.

For identification of the dominant frequency, each mean frequency spectrum was smoothed by the method of "smoothing by threes": for each spectral point, the computer summed half its amplitude value with one quarter of the amplitude value of each of the two adjacent points. This process was repeated 23 times. From the smoothed spectrum the dominant peak was identified as the peak of greatest amplitude and the frequency of this dominant peak was determined.⁸

Analysis of plasma catecholamines

Catecholamines were extracted from plasma using a two-stage cation exchange and diphenyl borate extraction process and measured by high-performance liquid chromatography with electrochemical detection.⁶ All samples from a single infusion on one subject were measured in the same assay batch. The lower limits of detection of this assay were 0.05 nmol l⁻¹ for both adrenaline and noradrenaline. The intra-assay coefficients of variation at baseline levels of catecholamines were noradrenaline (1.5 nmol l⁻¹) 6%, adrenaline (0.2 nmol l⁻¹) 9%. The interassay coefficients of variation were noradrenaline 9%, adrenaline, 20%.

Statistical analysis

Statistical analysis of these results used standard analysis of variance (ANOVA) methods. Where F tests revealed significant differences between treatments, differences were identified by *t* tests on the contrasts in the group means.

Results

Plasma catecholamines

The means of the pre-infusion plasma adrenaline concentrations on the three separate occasions were: saline, 0.16 ± 0.03; adrenaline-10, 0.19 ± 0.02; adrenaline-50, 0.15 ± 0.04 nmol l⁻¹. During the low dose infusion of adrenaline (adrenaline-10) the plasma adrenaline rose to a peak mean of 0.77 ±

0.08 nmol l⁻¹ and during the high dose infusion (adrenaline-50) to 2.28 ± 0.12 nmol l⁻¹. These peak concentrations were significantly different (ANOVA *p* < 0.001). By 15 and 30 minutes after cessation of the infusions plasma adrenaline levels had returned to basal values. Venous noradrenaline concentrations during adrenaline infusions were slightly but significantly higher (range 1.27 to 1.52 nmol l⁻¹) than pre-infusion levels (1.18 to 1.38 nmol l⁻¹) (ANOVA *p* < 0.01).

Tremor

The effect of adrenaline on tremor amplitude expressed as overall (0–50 Hz) rms acceleration is shown in fig 1. After 5 minutes infusion of adrenaline-50, tremor amplitude increased from 0.18 ± 0.03 to 0.33 ± 0.07 ms⁻² (mean ± SEM) and by 25 minutes the mean rms acceleration had increased to 0.61 ± 0.18 ms⁻² (*p* < 0.01 compared with control infusion). Tremor amplitude had returned to pre-infusion levels 20 minutes after the end of the infusion. Overall tremor amplitude did not increase significantly during the adrenaline-10 infusion nor during the saline infusion.

Figure 2 shows the mean tremor spectra for the six subjects measured during the saline, adrenaline-10 and adrenaline-50 infusions. The variation in the response between subjects is indicated by the broken lines representing the standard error of the mean. The small increase in tremor amplitude in the 8–11 Hz band during the adrenaline-10 infusion was not significantly different from the control infusion although in three of the six subjects tremor amplitude did increase. The higher dose of adrenaline produced a statistically significant increase in tremor (8–11 Hz and 0–50 Hz *p* < 0.01). There was considerable variation in the magnitude of the response between subjects as indicated by the large standard errors but tremor amplitude was enhanced in all six subjects at that dose.

There were no significant shifts when the frequencies of the dominant peaks for the control, adrenaline-10 and adrenaline-50 measurements were compared.

Discussion

Physiological tremor is increased by endogenously produced adrenaline, in stress and anxiety,^{9,10} hypoglycaemia and during exercise, and during intravenous administration of adrenaline.⁵ This study confirms the latter observation and provides further information regarding the levels of adrenaline required to produce detectable changes in the tremor spectrum.

Marsden *et al*⁵ infused adrenaline at a rate of

Fig 1 Overall rms acceleration (0–50 Hz) before, during and after infusions of saline (●), adrenaline 10 ng.kg⁻¹.min⁻¹ (○) and adrenaline 50 ng.kg⁻¹.min⁻¹ (△) **p* < 0.05, ***p* < 0.01 for differences from saline infusion.

Fig 2 Mean frequency spectra over the range 0–25 Hz (± 1 SEM) for 6 subjects showing the changes occurring during the 25th minute of an infusion of saline (left), adrenaline $10 \text{ ng kg}^{-1} \text{ min}^{-1}$ (middle) and adrenaline $50 \text{ ng kg}^{-1} \text{ min}^{-1}$ (right).

$10 \mu\text{g/min}$ and we estimate that this would have produced venous concentrations of $5\text{--}6 \text{ nmol l}^{-1}$, that is three times greater than in the present study. It has recently become possible to determine accurately the low concentrations of adrenaline in the blood seen in physiological situations such as in the supine and standing positions and during exercise.^{11–13} The doses used in this study resulted in measured venous concentrations of 0.8 nmol l^{-1} (adrenaline-10) and 2.3 nmol l^{-1} (adrenaline-50) and were similar to the concentrations found on standing^{11,12} and after exercise (heart rate 158 bmin^{-1}).¹³ In this study the higher dose produced concentrations at the upper end of the physiological range achieved from endogenous adrenaline release which are likely to have been 3–25 times lower than the levels investigated in other tremor studies.^{2–5}

Our results demonstrate that enhancement of plasma levels of adrenaline to levels similar to those seen during exercise caused a broad frequency band rise in tremor amplitude. Smaller increases in circulating adrenaline such as those which might occur

when changing from a supine to a standing position were not sufficient to cause a consistent rise in tremor amplitude in an 8–11 Hz frequency band. In more sensitive subjects an increased tremor may be seen since tremor increased in three of our subjects at the low dose of adrenaline.

Marsden *et al* showed that peripheral β -adrenoceptors located in the forearm were responsible for the increase in tremor elicited by β -agonists.⁵ Adrenaline has other metabolic and haemodynamic effects on skeletal muscle. These same doses of adrenaline caused a reduction in vascular resistance¹⁴ which could alter the visco-elasticity of the muscle and therefore its natural resonance and filtering properties. Lactate levels in the muscle increase when adrenaline concentrations in the blood exceed 1.2 nmol l^{-1} .^{14,15} Fellows *et al*¹⁴ have shown that plasma potassium concentration falls during an infusion of adrenaline $50 \text{ ng kg}^{-1} \text{ min}^{-1}$. These metabolic effects may be important in the mechanism producing an increase in tremor when plasma adrenaline concentrations rise. The plasma adrenaline thresholds

for metabolic actions are higher than for cardiac chronotropic effects.^{14,15} The tremogenic threshold for adrenaline though not precisely determined in this study appears to be at the lower plasma concentration (0.6 nmol l^{-1}) which is in the range which causes tachycardia. The venous levels of adrenaline required to produce measurable effects on tremor have been found to be within the physiological range.

References

- ¹ Barcroft H, Peterson E, Schwab RS. Action of adrenaline and noradrenaline on the tremor in Parkinson's disease. *Neurology (Minneapolis)* 1952;**2**:154–60.
- ² Constan C. The effects of adrenaline, noradrenaline and isoprenaline on Parkinsonian tremor. *J Neurol Neurosurg Psychiatry* 1962;**25**:116–21.
- ³ Owen DAL, Marsden CD. Effect of adrenergic β -blockade on Parkinsonian tremor. *Lancet* 1965;**ii**:1259–62.
- ⁴ Marshall J, Schneiden H. Effect of adrenaline, noradrenaline, atropine and nicotine on some types of human tremor. *J Neurol Neurosurg Psychiatry* 1966;**29**:214–8.
- ⁵ Marsden CD, Foley TH, Owen AL, McAllister RG. Peripheral β -adrenergic receptors concerned with tremor. *Clin Sci* 1967;**33**:53–65.
- ⁶ Macdonald IA, Lake DM. An improved technique for extracting catecholamines from body fluids. *J Neurosci Methods* 1985;**13**:239–48.
- ⁷ Birmingham AT, Williams EJ, Wilson CG, Wright P. Finger tremor in normal subjects *J Physiol (Lond)* 1977;**276**:20–21P.
- ⁸ Birmingham AT, Wharrad HJ, Williams EJ, Wilson CG. Accelerometric measurements of finger tremor: analysis of the analogue signal. *J Physiol (Lond)* 1985;**361**:12P.
- ⁹ Graham JDP. Static tremor in anxiety states. *J Neurol Neurosurg Psychiatry* 1945;**8**:57–60.
- ¹⁰ Tyrer P, Lader MH. Tremor in acute and chronic anxiety. *Arch Gen Psychiatry* 1974;**31**:506–10.
- ¹¹ Warren JB, O'Brien M, Dalton N, Turner CT. Sympathetic activity in benign familial tremor. *Lancet* 1984;**i**:461–2.
- ¹² Cryer PE. Isotope derivative measurements of plasma noradrenaline and epinephrine in man. *Diabetes* 1976;**25**:1071–82.
- ¹³ Warren JB, Dalton NA. A comparison of the bronchodilator and vasopressor effects of exercise levels of adrenaline in man *Clin Sci* 1983;**64**:475–9.
- ¹⁴ Fellows IW, Bennett T, Macdonald IA. The effect of adrenaline upon cardiovascular and metabolic functions in man. *Clin Sci* 1985;**69**:215–22.
- ¹⁵ Clutter WE, Bier DM, Shah SD, Cryer PE. Epinephrine plasma metabolic clearance rates and physiological thresholds for metabolic and hemodynamic actions in man. *J Clin Invest* 1980;**66**:94–101.