Adrenergic beta-receptor sensitivity in essential tremor

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SUMMARY Adrenergic beta-receptor sensitivity of six male patients with essential tremor and six age-matched normal controls was assessed by measuring the response in the heart rate and postural tremor to incremental injections of the adrenergic beta-agonist isoprenaline. The relative increase in heart rate and tremor in essential tremor patients did not differ from that in normal controls. It is concluded that no major abnormality is likely to exist in the peripheral adrenergic beta-receptor sensitivity in essential tremor.

The pathophysiology of essential tremor is not known. A functional difference in adrenergic neurotransmission could exist in this disease since adrenergic beta-receptor antagonists reduce tremor amplitude in the majority of patients. An attempt was therefore made to analyse beta-receptor sensitivity in patients with essential tremor known to respond favourably to propranolol.

Material and methods

Six male patients with essential tremor were studied. They were 20-48 years of age (mean 40). The results were compared with observations on six normal volunteers 26-59 (mean 39.5) years of age. Four of the patients had a family history of tremor and three had noticed that alcohol suppressed the tremor. All responded to oral non-selective beta-adrenoceptor agonist medication. All the subjects studied had given informed consent to their participation after explanation of the procedures and potential risks involved.

Peripheral adrenergic beta-receptor sensitivity was estimated by administering varying concentrations of isoprenaline hydrochloride intravenously using the method described by Cleaveland *et al.*¹ Different concentrations of the drug were injected rapidly into the left cubital vein of supine subjects. Injections were started with a low dose (0.25 µg), which was then doubled until an increase of about 30 beats per minute (bpm) in the heart rate was obtained. Saline-placebo injections were given intermit-

tently. Throughout the test the ECG was monitored using standard recording techniques. In addition, a computer was used to measure the RR intervals for 30 seconds before and 1.5 minutes after the isoprenaline injection, to calculate the relative increase in the heart rate and to give a graphic display of the RR intervals converted to the bpm value throughout the follow-up period (fig 1). Chronotropic dose (CD₂₅), defined as the dose of isoprenaline HCl in µg needed to increase the heart rate by 25 beats per minute, was calculated from these figures.¹ The CD₂₅ was considered to give one estimate of the adrenergic beta-receptor sensitivity of subjects studied, though mostly of the beta-1 receptors. A parameter presumed to reflect adrenergic beta-2-receptor sensitivity, at least to some extent, was based on evaluation of the tremor enhancement, caused by isoprenaline injections, which is known to occur in both normal subjects^{2,3} and essential tremor patients.^{4,5} Postural tremor of the subjects' right hand was recorded with a Grass SPA accelerometer attached to the middle finger while the subjects held their hand elevated horizontally. The tremor signal was amplified, full-wave rectified, and integrated in 10 s periods to obtain a cumulative value of tremor. The subjects were asked to raise their arm repeatedly for a period of 30 to 40 s, followed by a rest period of about 30 s. The average of the two to three 10 s periods thus obtained was used as a value for the tremor intensity at a given time. An example of such an experiment is shown in fig 2. At least two recordings were obtained before the injections. The recordings were continued as described for four to five minutes after the injections. During this period the enhanced tremor had already decreased to a variable degree, the peak values being obtained between 1.5 and 3.5 minutes after the injections. Thereafter, the tremor recordings were individually controlled until the amplitude had reached the pre-injection level. This occurred within 15 minutes, the time being longer with higher isoproterenol dosages. Student's *t* test was used in statistical evaluations.

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Fig 1 Computer print-out of tachycardia in a patient with essential tremor given an injection of 4 μ g isoprenaline HCl iv at the beginning of the display. Heart rate began to increase about 20 s after the injection. Small fluctuations in the response represents beat-to-beat variation of the heart rate induced by respiration (respiratory sinus arrhythmia). The duration of the print-out is about one minute.

Fig 2 Continuous recording of postural tremor in a patient who was given 5 μ g isoprenaline HCl at the time illustrated. At that point the subject raised his hand horizontally for about 40 s, followed by a rest of some 20 s. Two additional periods of tremor recordings are illustrated by arrows. The patient's tremor is shown below the time scale. The lower scale shows the cumulative tremor intensity over 10 s periods throughout the recording.

Results

Isoprenaline injections caused a dose-dependent increase in both the heart rate and tremor amplitude in both the normal subjects and essential tremor patients. The increase in the heart rate began about 25 s after the injection and reached a maximum about 20 s later (fig 1). Tremor intensity increased between 1 and 1.5 minutes, reaching maximum values between 1.5 and 3 minutes after isoprenaline injections. Figure 2 illustrates an actual recording from a patient with essential tremor given 5 μ g of

isoprenaline hydrochloride iv. The effects of different isoprenaline dosages on tremor and the duration of tremor enhancement are illustrated in fig 3.

The CD_{25} value obtained for the essential tremor patients ($4.1 \pm 1.5 \mu$ g) did not differ from that calculation for the normal controls ($4.4 \pm 1.2 \mu$ g). Respective resting pulse rates were 77.0 ± 8.4 and 70.3 ± 6.4 bpm. On the other hand, the maximum intensities of the tremor after the isoprenaline injections were higher in the essential tremor patients (table) but so were the preinjection levels. The relative increase in the tremor was somewhat more pronounced in the patients (107%) than in the normal controls (91%), but the difference was not statistically significant.

Discussion

Essential tremor amplitude is greatly exacerbated by stress, excitement or fear, sympathomimetics and various stimulants such as coffee and tobacco. Apart from the known hereditary disposition the pathophysiological mechanisms of essential tremor are obscure. Marshall⁶ proposed that essential tremor is an exaggerated form of physiological tremor involving oscillations within the peripheral reflex arch. Contributions by the central nervous system are indicated by the fact that stereotaxic operations on the brain relieve tremor⁷⁻⁹ and that it disappears from the hemiplegic side following a stroke.^{8,10} Oscillation in the olivorubrocerebellar loop has been proposed to be of importance.^{11,12} Patients benefit to a limited extent only from minor tranquilisers,¹³ apparently more from primidone¹⁴⁻¹⁶ and especially from ethyl alcohol.¹⁷

Fig 3 The figure is a summary of recordings of tremor intensity at a one minute intervals over a period of 10 minutes each in a patient given three different dosages of isoprenaline HCl intravenously. Increase in tremor amplitude occurred after one minute, that is later than the increase in the heart rate (fig 1).

Table Effect of iv isoprenaline HCl on postural tremor (mean $\pm$ SD) in essential tremor patients and normal subjects

	Unstimulated tremor	Isoprenaline tremor	Isoprenaline dose (μ g)	% increase of tremor per 1 μ g isoprenaline
Patients	7.1 $\pm$ 2.4	32.3 $\pm$ 8.7	4.5 $\pm$ 0.5	107 $\pm$ 25
Normal subjects	2.2 $\pm$ 0.4	9.0 $\pm$ 2.9	4.5 $\pm$ 0.8	91 $\pm$ 11

Adrenergic beta-blocking drugs have been the treatment of choice for more than ten years, the non-specific blockers being more effective than the cardioselective ones.¹⁷ The observation that alpha-adrenergic blocking drugs also suppress essential tremor¹⁸ awaits confirmation. The therapeutic effect of the adrenergic beta-blocking drugs in essential tremor^{17 19 20} could theoretically be based on functional differences in the receptor sensitivity of essential tremor patients compared to normal subjects. The present results indicate that there are no major differences between patients and normal volunteers in the cardiovascular beta-receptor sensitivity measured as chronotropic response to intravenous isoprenaline hydrochloride. Further more, the relative increases in the postural tremor of the patients and the normal volunteers were of roughly the same magnitude. These results are interpreted to indicate that adrenergic beta-receptor sensitivity is within normal limits in patients with essential tremor. This interpretation is limited to the cardiovascular system and to the part of the motor system accessible to intravenous isoprenaline. The present study cannot exclude the possibility that differences exist in the adrenergic beta-receptor sensitivity in the central nervous system since isoprenaline hydrochloride is not believed to cross the blood-brain barrier. Another theoretical possibility is that isoprenaline may not penetrate the capsule surrounding muscle spindles which may or may not contain adrenergic beta-receptors.

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