response to hypoglycaemia develops in addition to an "unawareness" of hypoglycaemic symptoms.[13] The presence of autonomic dysfunction could thus exaggerate the problems caused by metabolically mediated hypoglycaemia in some SIDS cases. Factors such as a falling ambient temperature, which exaggerate autonomic dysfunction, would increase the risk of death. Further studies are needed to assess prospectively the predictive value of autonomic function tests for sudden unexpected deaths in infants and the effect of the associated epidemiological factors on the results.

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TREATMENT OF NARCOLEPSY WITH L-TYROSINE: DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL

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Summary A randomised, double-blind, placebo-controlled study of L-tyrosine was done in ten subjects with narcolepsy and cataplexy. Of twenty-eight visual analogue scales rating mood and arousal, the subjects' ratings in the tyrosine treatment (9 g daily) and placebo periods differed significantly for only three (less tired, less drowsy, more alert). Ratings of daytime drowsiness, cataplexy, sleep paralysis, night-time sleep, overall clinical response, and measurements of multiple sleep latency and tests of speed and attention did not differ significantly between tyrosine and placebo periods. Dietary supplementation with tyrosine 9 g daily for 4 weeks seems to have a mild stimulant action on the central nervous system but this effect is not clinically significant in the treatment of the narcoleptic syndrome.

Introduction

Mouret and colleagues reported last year that L-tyrosine was of benefit in the narcoleptic syndrome.[1] Their results are of substantial interest, since they imply an abnormality of catecholamine neurotransmission in narcolepsy. Since dietary supplementation with L-tyrosine has few or no side-effects, this treatment would be a major therapeutic advance if efficacy were confirmed. However, the study by Mouret et al was open, and no placebo preparation or control population was used. We have done a double-blind, crossover study, comparing L-tyrosine with placebo in ten subjects with the narcoleptic syndrome.

Patients and Methods

We studied six women and four men, mean age 42 years (range 27–56), attending King's College Hospital Sleep Disorders Clinic, who had an established diagnosis of the narcoleptic syndrome. All had narcolepsy and periods of automatic behaviour. The onset was gradual in eight subjects and rapid in two, starting between the ages of 12 and 37 years (mean 21). Nine patients had cataplexy, severe in three, moderate in one, and mild in five. Six subjects, including the patient who did not have cataplexy, had sleep paralysis. Five subjects underwent HLA typing; all five were positive for DR2/DQw1.

Three patients were receiving no treatment for narcolepsy-cataplexy at the start of the study. Four were taking mazindol, 2–10 mg daily, and two dexamphetamine, 7·5 mg and 30 mg, respectively, for treatment of narcolepsy. Three were taking clomipramine, 10–100 mg daily, and one clonazepam, 1·5 mg daily, for treatment of cataplexy. One patient was taking atenolol, 50 mg daily, for control of hypertension. The dosage and timing of established treatments were not changed during the trial. Ethical committee approval was obtained and each patient gave written consent.

Patients were randomised to L-tyrosine 9 g daily, given in three equal divided doses, or an identical number of matched placebo capsules containing lactose. Active and placebo preparations were given for two consecutive 4-week periods, with no wash-out period.

To assess daytime drowsiness a multiple sleep latency test was carried out, with the protocol of the Stanford Sleep Disorder Clinic.[2] Subjects were instructed to try to go to sleep in a quiet, darkened room every 2 h between 1000 h and 1800 h. Mean values of the time from lights out to stages 1 and 2 sleep and latency to the onset of rapid eye movement (REM) sleep were measured before treatment and during treatment weeks 4 and 8 in all subjects. Subjective assessment of the changes in severity of narcolepsy and cataplexy and overall response to treatment were graded on a scale of 1–5. Night-time sleep, daytime sleep attacks, cataplexy, sleep paralysis, and dreaming were measured by the King's College Hospital sleep clinic narcolepsy severity rating scale which is sensitive to drug effect in narcolepsy.[3] In addition to clinical examination, a battery of neuropsychological tests were carried out in four patients, testing speed and attention. Six tests were used, which when combined gave a speed quotient that is a measure of alertness.[4] The subjects also did the digit symbol subtest of the Wechsler Adult Intelligence Scale-Revised[5] and the Trail Making Test.[6] All subjects completed a self-administered questionnaire before starting the trial and on the same day every week throughout

the study. Changes in mood, arousal, and sleepiness were measured on 100 mm validated visual analogue scales developed by the MRC Applied Psychology Unit in Cambridge.[7] Composite scores were evaluated for the tyrosine and placebo periods.

Statistical significance was assessed by means of the Wilcoxon matched-pairs signed-ranks test and Student's *t* test.

Of the ten patients entered, one reported a pronounced deterioration in both cataplexy and narcolepsy 5 days after starting the second treatment period. The code was broken and he was found to have been taking placebo and then tyrosine. The cataplexy was so severe as to interfere with his work, and required a higher dose of clomipramine; he was withdrawn from the study. The results are based on the nine patients who completed the trial.

Results

Three of the sixteen subjective rating scales for measures of arousal differed significantly between tyrosine and placebo periods. Patients rated themselves as less tired ($p < 0.05$), less drowsy ($p < 0.01$), and more alert ($p < 0.05$) while on tyrosine. There were no significant differences between the tyrosine and placebo periods in the remaining arousal rating scales, or in the twelve rating scales for mood.

None of the clinical variables on night-time sleep, daytime drowsiness, cataplexy, or sleep paralysis differed significantly between tyrosine and placebo periods (see table). Mean values of the time to stage 2 sleep and latency to the onset of REM sleep were slightly but not significantly higher during tyrosine than during placebo. Latency to stage 1 sleep did not change.

There were no significant differences in the results of psychometric tests measuring speed and accuracy (mean [SEM] speed quotient 115 [8] on tyrosine *vs* 114 [7] on placebo), in the digit symbol test (mean [SEM] correct responses 66 [15] *vs* 70 [12]), or in the trail-making test (mean [SEM] time 73 [28] *vs* 57 [20] s).

Clinical scores (1 = much better; 2 = slightly better; 3 = no change; 4 = slightly worse; 5 = much worse) for narcolepsy (3·0 [1·6] *vs* 2·7 [1·4]), cataplexy (3·5 [0·9] *vs* 2·5 [1·2]), and overall response (2·9 [1·5] *vs* 2·9 [1·3]) did not differ between tyrosine and placebo periods and no order effects were seen. Three patients reported a preference for tyrosine, four for placebo, and two expressed no preference.

The three subjects who felt they improved on tyrosine rated themselves as less tired ($p < 0.01$), less drowsy ($p < 0.01$), and more alert ($p < 0.05$), but none of the clinical variables were significantly better than those during placebo. In these three subjects latency to onset of REM sleep was no longer during treatment with tyrosine than during placebo treatment. Times to onset of stages 1 and 2 sleep were not affected.

There were no differences in results between the three subjects who were on no treatment before entering the trial and those who were taking stimulant drugs or clomipramine. Patient self-rating scores of mood, arousal, and severity of narcolepsy were not significantly different during weeks 1 and 4 of tyrosine treatment. Headache, irritability, and difficulty in falling asleep were not reported.

SLEEP LATENCY AND CLINICAL RESPONSE

—	Mean (SEM) for all patients		
	Before treatment	Tyrosine	Placebo
Sleep latencies			
Time to stage 1 sleep (s)	601 (593)	374 (254)	363 (316)
Time to stage 2 sleep (s)	758 (178)	788 (184)	713 (126)
REM latency (s)	751 (279)	729 (251)	643 (293)
Night-time sleep			
Duration (h)	7·1 (1·7)	7·5 (1·2)	7·6 (1·9)
No of wakings	2·3 (1·2)	2·6 (2·0)	3·7 (2·8)
Daytime sleep			
No of naps/day	3·5 (1·9)	4·1 (3·0)	3·9 (2·1)
Duration (min)	88·3 (59·0)	99·5 (52·0)	101·8 (44·0)
No of half-asleep periods per waking day	2·9 (2·2)	2·8 (2·1)	2·6 (2·2)
Cataplexy			
No of attacks/24 h	4·2 (4·5)	4·5 (3·0)	3·4 (2·9)
Duration of attacks (s)	64·4 (73·6)	48·3 (39·3)	36·9 (29·0)
Sleep paralysis			
No of attacks/wk	1·9 (3·1)	2·2 (2·6)	2·5 (2·9)

Discussion

Little is known of the possible effects of tyrosine on brain function. In animals oral or intraperitoneal injection of tyrosine may increase aggression and induce behavioural abnormalities similar to those seen after amphetamine administration.[8,9] Tyrosine also reduces blood pressure in hypertensive rats, possibly by acting on central noradrenaline receptors.[10] In man attention deficit disorders do not improve with tyrosine,[11] but some patients with depressive illness may benefit.[12,13] In our subjects with narcolepsy, dietary supplementation with tyrosine may have had a slight stimulant action on the central nervous system as judged by greater levels of arousal on self-administered visual analogue scales. However, other measures of arousal, including clinical assessment, psychometric testing, and sleep latency, did not change.

The mechanism by which tyrosine may have slight stimulant action in narcolepsy is unknown. Most of an oral dose of tyrosine is catabolised initially by tyrosine aminotransferase in the liver.[14] However, some is metabolised to tyramine, either by dopa-decarboxylase[15] or by tyrosine decarboxylase, which is found in microorganisms, including *Streptococcus faecalis*.[16,17] Tyramine acts as an indirect sympathomimetic agent[18] and its formation may bring about any stimulant effect of tyrosine. Tyramine causes release of catecholamines from the brain similar to that seen after amphetamine administration.[19,20] Tyrosine is transported into the brain by a saturable carrier mechanism for large neutral aminoacids and changes in dietary tyrosine could induce complex changes in the availability of other aminoacids to neurons.[21] Catecholamine synthesis is unlikely to be affected by the precursor supply of tyrosine, since tyrosine hydroxylase is rate-limiting and usually saturated.[21]

Three of our patients said they had less daytime drowsiness and one patient that cataplexy was less severe on tyrosine. The changes, however, were mild and of dubious clinical significance. Four patients said they were worse on tyrosine and two reported no difference between tyrosine and placebo. We could not replicate the findings of Mouret and colleagues;[1] all their narcoleptic subjects became free of symptoms while taking tyrosine. Cataplexy was abolished in a few days although daytime drowsiness took longer, up to 6 months, to improve. Their study was open and no placebo or controls were used. Some of their subjects had a coexistent depressive illness, and despite the apparent cure, objective measures of sleep latency showed no improvement during treatment with tyrosine.

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Preliminary Communications

RAPID DIAGNOSIS OF TUBERCULOSIS BY AMPLIFICATION OF MYCOBACTERIAL DNA IN CLINICAL SAMPLES

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Summary A method based on DNA amplification and hybridisation for the rapid detection of *Mycobacterium tuberculosis* was used to test 35 clinical specimens (sputum, gastric aspirate, abscess aspirate, biopsy sample) from 34 patients in whom tuberculosis was suspected. *M tuberculosis* was detected in 15 specimens, 2 of which were negative by standard microbiological criteria (microscopy and/or culture). 20 specimens, negative by standard methods, were also negative by the amplification method. *M tuberculosis* was also detected in peripheral blood samples of 2 of 4 patients with AIDS from whom the organism had been isolated.

INTRODUCTION

DIAGNOSIS of mycobacterial infections is a long and tedious process: identification and antibiotic sensitivity testing can take up to 10 weeks because of the slow growth rate of mycobacteria; and direct microscopy, though rapid and convenient, is insensitive because clinical samples may contain only a few organisms.[1] Consequently, the start of treatment may be delayed, or inappropriate empiric therapy for *Mycobacterium tuberculosis* may be given to patients without mycobacterial infections or to those who are infected with atypical mycobacteria that are unresponsive to such treatment—eg, immunocompromised patients.

An alternative approach is the use of DNA probes,[2,3] but their low sensitivity limits their application to cultured bacteria.[4] We have lately described a method based on DNA amplification and hybridisation that could be applied to the rapid diagnosis of mycobacterial infections.[5] This procedure has already been used to diagnose genetic diseases,[6] and viral[7] and bacterial[8] infections. For the detection of mycobacteria, a 383-base-pair DNA fragment (located within the gene that encodes the 65 kD mycobacterial antigen) is amplified for all mycobacterial species. The amplified fragment is then hybridised to species-specific oligonucleotide probes which can specifically identify the *M tuberculosis* complex, the *M avium-intracellulare* complex, and *M fortuitum*. Successive dilutions of Bacille Calmette-Guérin (BCG) bacilli in 10^6 eucaryotic cells indicated that less than 10 bacilli per sample could be detected with this method.[5]

We now report the use of this technique to detect and identify *M tuberculosis* directly in clinical specimens, including peripheral blood samples from patients with AIDS.

COMPARISON OF THE AMPLIFICATION PROCEDURE WITH ROUTINE TECHNIQUES FOR DETECTION OF MYCOBACTERIUM TUBERCULOSIS IN CLINICAL SPECIMENS

Results of amplification procedure	Specimen	Results of routine procedures (n)		
		Direct exam positive/ culture positive	Direct exam negative/ culture positive	Direct exam negative/ culture negative
Positive for *M tuberculosis*	Sputum (6)	5	1	0
	Gastric aspirate (5)	1	2	2*
	Lymph node biopsy (3)	3	0	0
	Abscess aspirate (1)	1	0	0
Negative for *M tuberculosis*	Sputum (11)	0	0	11
	Gastric aspirate (8)	0	0	8
	Lymph node biopsy (1)	0	0	1

*Both specimens from a patient with recently documented tuberculosis who had been receiving anti-tuberculous therapy for 4 weeks.
Numbers in parentheses indicate no of samples.
exam = microscopic examination after Ziehl-Neelsen staining.

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