Effects of oral amines on the EEG

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SUMMARY Oral tyramine activated pre-existing episodic EEG abnormalities—namely, sharp waves, spike and wave, and localised theta activity—in epileptic patients. Little change was found in the EEGs of migraineous subjects after chocolate or beta-phenylethylamine. The implications of the findings with tyramine are discussed.

In our earlier studies on groups of patients with migraine, dietary migraine, and with migraine and epilepsy, it was shown that the administration of oral tyramine increased pre-existing EEG abnormalities (Scott et al., 1972). This EEG activation was observed both in patients whose migraine was apparently precipitated by the ingestion of foods containing tyramine and in patients who had both migraine and epilepsy, but not in those whose migraine was unrelated to dietary factors. The EEG changes consisted principally of an increase in the amount of episodic slow activity and sharp components over the temporal areas. These findings, and the observation that tyramine activated experimental epileptic foci in monkeys (Scott et al., 1972), have led us to investigate the effect of oral tyramine on the EEG of patients with epilepsy alone, using a similar design to that of our previous studies. Preliminary results have been reported elsewhere (Swash et al., 1975).

Although patients with migraine frequently report that chocolate seems to precipitate their headache (Hainington et al., 1970), a double-blind investigation of the effect of chocolate in triggering migraine headache in susceptible patients did not confirm this effect of chocolate (Moffett et al., 1974). In the present study EEG recordings were made after ingestion of chocolate and after placebo. In addition, a similar group of patients were given beta-phenylethylamine, the amine present in chocolate and considered to be important in migraine (Sandler et al., 1974; Chaytor et al., 1975). Here EEGs were also performed.

In this report we shall describe the detailed EEG results in these groups of patients and discuss the implications of the results.

Clinical methods

TYRAMINE AND EPILEPSY

Fifteen patients with epilepsy were studied (Swash et al., 1975). Their ages ranged from 16 to 63 years (mean 36 years). There were eight patients with idiopathic epilepsy and six with temporal lobe epilepsy. The remaining patient had Jacksonian seizures. All had at least one fit every month. They had been attending the neurological clinic at The London Hospital for treatment of their epilepsy for many years. There was no history of migraine or of any relationship between food substances and their seizures. The patients continued anticonvulsant therapy throughout the investigation. They were given tyramine hydrochloride 125 mg or its matching lactose placebo, in capsule form, at an interval of a week using a balanced, double-blind design. Each patient then had an EEG recorded about four to five hours after ingesting each capsule.

CHOCOLATE AND MIGRAINE

Ten migraineous subjects whose ages ranged from 34 to 62 (mean 41) years were studied. These patients were carefully selected to include only those with definite classical migraine, who had excluded cocoa-containing products from their diet because they were certain that these precipitated their headaches. They continued their regular anti-migraine medication, if any, throughout the investigation. These patients were given a bar of chocolate weighing 44 g and its matching placebo in a balanced double-blind design. The chocolate bars contained approximately 18 g of cocoa solids, and were similar to those used in a previous investigation (Moffett et al., 1974). These, and the placebo bars were administered at intervals of at least a week. Approximately five hours after ingestion an EEG was recorded.

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A second group of 10 migrainous subjects, whose ages ranged from 42 to 62 years (mean 51 years) all of whom had classical migraine and who had excluded cocoa-containing products from their diet because they were certain that these precipitated their migraine, were studied. For these patients a similar design was used but capsules containing beta-phenylethylamine 3 mg or its matching lactose placebo were given. EEG recordings were made about five hours after each capsule had been ingested.

EEG methods

The EEGs were recorded on Elema Schönander apparatus using a standard technique. As far as possible the two records on each patient were made by the same technician using the same apparatus in the same room, at the same of day (Margerison et al., 1967). The electrodes were placed according to the international 10/20 system and transverse as well as average reference montages were employed. Hyperventilation was always carried out, as this had been frequently observed to potentiate abnormalities in our earlier studies on the effect of tyramine on the EEG of migrainous subjects (Scott et al., 1972).

When the studies had been completed, the pairs of EEGs from each patient were coded, masked, and rated without reference to whether the active or inactive substance had been administered. Ratings were carried out by M.S. and D.F.S. according to criteria established in previous investigations (Scott et al., 1972). Assessment of background activity and of the occurrence of paroxysmal features was made separately. The raters were asked to decide which of each pair of records was the more abnormal: this was subsequently related to ingestion of the active substance or its placebo. The occurrence of head-
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aches or epileptic attacks related to ingestion of the active substance or its placebo was also assessed at each visit and subsequently by a questionnaire, returned in a stamped, addressed envelope 48 hours later, as in previous studies (cf. Moffett et al., 1972).

Results

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Agreement was reached as to which of the pair of EEGs was the more abnormal in 14 of the 15 epileptic patients. In the remaining patient no difference could be discerned between the records made after tyramine and placebo. In 11 of the 14 pairs of records the more abnormal EEG was that made after tyramine (p < 0.01). In these 11 patients the pre-existing EEG abnormalities were markedly accentuated (Figs. 1, 2, and 3). This effect was more pronounced during and after hyperventilation (Fig. 4) so that focal sharp waves and bursts of atypical spike and wave as well as paroxysms of slow activity became more prominent, especially over the temporal areas. There was little effect on background activity. No patient experienced a seizure in the 24 hours after capsule ingestion.

CHOCOLATE AND MIGRAINE

In four of the 10 subjects the EEGs recorded after chocolate were more abnormal than after placebo; in four there was no change, and in two the record was found to be more abnormal after placebo. These differences did not reach significance. All four patients whose EEGs were rated as activated after chocolate tended to have disorganised background activity with episodic theta activity, sharply contoured theta forms, and a few sharp waves (Fig. 5). These abnormalities were mildly accentuated by overbreathing.

Fig. 2 A 40 year old patient with temporal lobe epilepsy. The EEG taken after placebo (P) shows left temporal sharp waves but after tyramine (T) there is not only sharp wave activity but a widespread disturbance of slow wave type appears mainly over the left hemisphere.
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In five of the 10 patients the EEG recorded after beta-phenylethylamine was assessed as the more abnormal of the pair (Fig. 6). In three no difference could be discerned between the two records and in two the EEG made after placebo was rated as the more abnormal. In each of these patients the differences between the two records was slight, consisting, in three of the five EEGs activated by beta-phenylethylamine, of sharpened theta forms and sharp wave episodes. There was some accentuation in two of these patients during hyperventilation.

Discussion
Our earlier studies with oral tyramine in various groups of migrainous patients showed that pre-existing EEG abnormalities were increased in all but the non-dietary group (Scott et al., 1972). However, we were unable to demonstrate that tyramine induced migrainous headache in these patients (Moffett et al., 1972). Similarly, we have found that chocolate failed to induce migrainous headache, even in apparently susceptible subjects, when investigated in a double-blind study (Moffett et al., 1974). In the present investigation the effects both of chocolate and of beta-phenylethylamine on the EEG in these migrainous subjects have been examined, as it has been suggested that beta-phenylethylamine is the active amine in chocolate (Sandler et al., 1974; Chaytor et al., 1975). However, as neither chocolate nor beta-phenylethylamine induced significant activation of pre-existing EEG abnormalities it must be concluded that tyramine has a different and more important effect on the central nervous system in migraine (Scott et al., 1972) than does chocolate or beta-phenylethylamine.

Since we have shown previously that tyramine accentuated the pre-existing abnormalities in patients suffering from both dietary migraine and migraine

![Fig. 3](http://jnnp.bmj.com/)  
A 25 year old patient with generalised fits. The resting EEG (P) taken after placebo capsule shows a mild abnormality consisting of sharp waves in the left temporal area. After tyramine (T) had been administered a burst of polyspike and wave is seen. This has a marked right-sided, post-central emphasis.
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with epilepsy (Scott et al., 1972) the next part of the present investigation has been concerned with the effects of tyramine on patients with epilepsy but without a history of migraine. In this group we have demonstrated that tyramine markedly increased abnormalities found in the resting EEG of a significant proportion of patients. Sharp waves, spikes, and spike and wave were particularly augmented. These are the EEG features found in the inter-ictal records of patients with frequent fits (Dawson et al., 1961; Rowan et al., 1975).

Although none of these patients experienced a seizure in the 24 hours after tyramine ingestion, one obvious possible implication of these findings is that tyramine may be an important factor in the biochemical changes associated with the induction of attacks in patients with epilepsy. There are other clues which suggest that tyramine or similar amines could be important in epilepsy—for example, tyramine is a substrate for monoamine oxidase in the central nervous system, and seizures can be precipitated in susceptible individuals by the administration of monoamine oxidase inhibitor drugs (Shepherd et al., 1968). Further, Chadwick et al. (1975) have reported increased monoamine metabolite concentrations in the CSF of epileptic patients, although these changes could have been due to anticonvulsant drugs. In addition, however, Shohmori et al. (1975) have observed reduced levels of monoamine oxidase in the circulating blood platelets of patients with epilepsy, some of whom were not receiving anticonvulsant medication. Clearly, further studies along these lines could prove of great interest.

Fig. 4 A 35 year old patient with generalised convulsions. Immediately after overbreathing, the placebo EEG (P) shows some post-central slow components. These occurred in a more generalised fashion and with greater profusion after tyramine (T) had been administered.
Fig. 5 A 54 year old migrainous patient whose attacks occurred after the ingestion of chocolate. The EEG after placebo (P) shows some irregularity with theta waves in the temporal channels. After eating chocolate (C) this was enhanced and was seen also on the opposite side. Some of the theta components on both sides had a sharpened outline.

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References


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![EEG diagram]

Fig. 6  A 51 year old migraine sufferer who had observed that chocolate precipitated attacks. The EEG after placebo (P) shows some sharp components in the left temporal region. These were slightly augmented and were seen over both temporal regions after the administration of beta-phenylethylamine (B).


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