Effect of chocolate in migraine: a double-blind study

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SYNOPSIS The effect of chocolate on a group of volunteer migrainous subjects, who had observed that headache regularly occurred after the ingestion of small amounts of cocoa products, was investigated. Two separate studies were carried out in a double-blind placebo controlled manner. Only 13 headaches occurred to chocolate alone in 80 subject sessions, and only two subjects responded consistently to chocolate in the two studies. This suggests that chocolate on its own is rarely a precipitant of migraine. Other possible implications of the results are also discussed.

The role of tyramine as a precipitating factor in migraine has been studied by Hanington (1967, 1969) and by Moffett *et al.* (1972), and it has been shown that there is a relationship between ingestion of tyramine-containing foods, headache, and electroencephalographic (EEG) changes. Furthermore, it is well known that chocolate, a substance which contains vasoactive amines (Hanington and Harper, 1968) is frequently incriminated as a cause of headache (see Hanington, 1969; Hanington *et al.*, 1970).

In order to examine the possible role of chocolate in migraine, we have studied its effect in a group of 25 patients using a double-blind, placebo controlled design. All these subjects had noticed that they were unable to eat even small quantities of chocolate or other cocoa products without suffering headache. In addition, we have investigated the role of other dietary factors in a larger group of subjects.

METHODS

All the subjects agreed to take part in the study, either as a result of an announcement in the *Journal* of the British Migraine Association indicating our interest in migraine precipitated by chocolate and asking for volunteers, or in response to a questionnaire subsequently included in this journal requesting information not only about dietary precipitants of migraine but also about the part played by alcoholic drinks. There were 332 respondents. The 88 subjects who had observed that chocolate seemed to precipitate their migraine were sent a more detailed questionnaire asking for information about the

relation of various foods, particularly chocolate, to their migraine and about the migrainous symptoms they usually experienced. From this group 25 subjects with classical migraine, 23 of whom were women, were selected. All of these subjects had found that even small amounts of chocolate precipitated their migraine. None was older than 65 years and none had hypertension. They continued their habitual anti-migrainous treatment but none was taking other medication. No dietary restrictions were imposed.

Two separate double-blind, fully balanced studies were performed, the first using chocolate and a matching placebo produced by Cadbury-Schweppes Limited and the second using chocolate and a matching placebo prepared by the London Hospital Pharmacy. Both placebos consisted of a synthetic fat which approximated in physical quality to cocoa butter but which was made from non-cocoa containing vegetable oils. To this were added sugar, colouring, and flavouring. The texture and taste of the real chocolate was disguised by additives. The detailed formulation of both types of chocolate and their matching placebos is given in an appendix.

The two studies will be described separately.

STUDY 1 The 25 selected subjects described above were studied. Their ages ranged from 22 to 62 years (mean 49 years). Each subject was sent two separate samples (Cadbury-Schweppes), the second two weeks after the first. One sample consisted of chocolate and the other of its matching placebo. The samples were of similar weight (approximately 44 g) and were identically wrapped in silver foil. The subjects were told only that they would be asked to eat two different sorts of chocolate. They were asked to respond by questionnaire 48 hours after eating the

chocolate, indicating whether or not they had experienced a headache, and if so, whether it was similar to their usual migraine. They were requested to return any uneaten portions of chocolate with their questionnaire so that there could be no direct comparison of the two samples: the second sample was not sent until this had been done. There was no direct contact between subjects and investigators at any time. When the study had been completed the questionnaires were assessed independently by two observers (M.S. and D.F.S.) as to whether headache had occurred and if so, whether it was similar to the migrainous headache described earlier by the patients in their questionnaires.

STUDY 2 Fifteen of the subjects who had taken part in study 1 took two additional samples of chocolate (London Hospital Pharmacy). These subjects' ages ranged from 22 to 62 years (mean 48 years). This experiment was designed in exactly the same manner as study 1. The samples of chocolate varied in weight (44 to 62 g) but care was taken to match the weight of the active preparation with the placebo in each case.

RESULTS

In study 1, 15 headaches occurred in 50 subject sessions; eight of these occurred after chocolate and five after placebo only. One subject had headache after both chocolate and placebo and 11 had no headache after either sample (Table 1).

TABLE 1
HEADACHES AFTER CHOCOLATE AND PLACEBO*

	<i>Chocolate only</i>	<i>Placebo only</i>	<i>Both</i>
<i>Study 1</i>			
11 subjects failed to respond with a headache to either	8	5	1
<i>Study 2</i>			
5 subjects failed to respond with a headache to either	5	3	1

* 1. Cadbury-Schweppes Samples, 25 subjects. 2. London Hospital Samples, 15 subjects.

In study 2, 10 headaches occurred in 30 subject sessions, five of these after chocolate only, three after placebo only, and one subject had headache after both chocolate and placebo. Six had no headache after either sample (Table 1).

Of the 15 subjects who took all four samples

TABLE 2
RESPONSE TO CHOCOLATE AND PLACEBO IN THE 15 SUBJECTS WHO TOOK PART IN BOTH STUDIES 1 AND 2

<i>Study 1</i>															
Subject	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Chocolate	-	-	-	-	-	-	+	+	+	+	+	-	-	-	-
Placebo	-	-	+	-	-	+	-	-	-	-	-	-	-	-	-
<i>Study 2</i>															
Chocolate	+	-	-	-	+	+	+	+	-	-	-	-	-	-	+
Placebo	+	-	-	+	-	-	-	-	+	+	-	-	-	-	-

Migraine +, No response -.

TABLE 3
ALCOHOL AND DIETARY QUESTIONNAIRE INFORMATION BASED ON 332 SUBJECTS

Percentage of subjects who reported alcoholic beverages and dietary factors as precipitants of migraine

Alcoholic beverages	
Spirits	61.4
Wines	64.5
Fortified wines	64.2
Beer	34.6
Food substances	
Citrus fruit	32.2
Chocolate	26.5
Cheese	13.3

only five responded consistently in both studies, two responded to chocolate alone on both occasions and three had no headache after any of the four samples. All the other subjects behaved differently in the two studies (Table 2).

OTHER DIETARY FACTORS AND ALCOHOL (Table 3) The questionnaire asking for information about dietary factors precipitating migraine, completed by 332 subjects, showed that spirits, fortified wines and wines were incriminated in about two-thirds of instances and beer in a third. Of the foods mentioned, citrus fruits were indicated in a third of the respondents, chocolate in a quarter, and cheese in a tenth. The combination of chocolate, alcohol, and citrus fruits was noted in a fifth of the 332 subjects. It is of interest that in our smaller group of 25 selected subjects, who took part in the chocolate studies, more than half reported that cheese as well as chocolate caused their migraine.

DISCUSSION

In this investigation 25 headaches were reported in 80 subject sessions but only 13 of these occurred after chocolate alone. Only two subjects responded to chocolate alone in both studies. This paucity of chocolate induced headache requires explanation. Either the subjects were incorrect in their observations, that chocolate played a part in the production of their headache or there were other contributing factors. The latter explanation seems the more likely and is suggested by the fact that all the subjects listed other causative agents. These were dietary factors, such as cheese, citrus fruits, or alcohol, or other factors such as stress, relaxation from stress, menstruation, fasting, or changes in medication.

The results of this study on the effect of chocolate are consistent with those noted in our earlier investigations with tyramine (Moffett *et al.*,

1972). In both studies when one particular factor—that is, either tyramine or chocolate—was isolated for study, the clinical observations both of the patients and their physicians that these dietary factors were important in the production of their migraine could not be confirmed. In our studies on the effect of tyramine, we showed, however, that EEG changes occurred in many subjects despite the absence of headache and it is possible that the EEG will provide a more sensitive measure of the effect of chocolate than the subjective development of headache (Scott *et al.*, 1972). In the questionnaire alcohol was often incriminated as a precipitant of migraine and it is possible that this may cause increased absorption of amines from the gut. The development of frank migraine may thus be the result not of a single factor, such as chocolate, tyramine, stress, or alcohol, but of several of these factors acting together in the susceptible individual.

APPENDIX

FORMULATION OF CHOCOLATE AND PLACEBO SAMPLES

STUDY 1: CADBURY-SCHWEPES LIMITED

<i>Chocolate</i>	% weight
Sugar	48.9
Cocoa mass—that is, roasted ground cocoa nib	32.6
Additional pressed cocoa butter	8.2
Rice flour (to match texture of placebo)	9.3
Emulsifier	0.5
Peppermint flavour	0.5
This chocolate contains the equivalent of 40.8% total cocoa solids (total fats 26.6%).	

<i>Placebo</i>	% weight
Sugar	33.0
Rice flour	33.0
Coberine (a partially hardened, non-cocoa butter, vegetable fat)	32.0
Colour	1.0
Emulsifier	0.5
Peppermint flavour	0.5

STUDY 2: LONDON HOSPITAL

<i>Chocolate</i>	% weight
Cocoa powder (Bourneville)	10
Powdered icing sugar (Tate and Lyle)	45
Oil of theobroma B.P.	35
Powdered lactose B.P.	10
This chocolate contains the equivalent of 45% total cocoa solids.	

<i>Placebo</i>	% weight
Powdered icing sugar	15
Powdered lactose B.P.	50
Extracoe (Loders and Nucoline Ltd.)	35
Imitation chocolate, mint (Anstead Ltd.) colouring	as necessary
Imitation chocolate Fl. 510313 (Soflor Ltd.) flavouring	as necessary
Imitation chocolate 'C' 3122011 (Food Inc. Ltd.)	as necessary

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