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Relationships between headache and amine changes after administration of reserpine to migrainous patients

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There is evidence that spontaneous migraine headache is associated with changes in 5-hydroxytryptamine (5HT) metabolism. Thus Sicuteri, Testi, and Anselmi (1961) reported grossly elevated urinary excretion of 5-hydroxyindoleacetic acid (5HIAA), the main urinary metabolite of 5HT, by migrainous subjects on days when attacks occurred. Increased excretion was also found by Curran, Hinterberger, and Lance (1965), although not at such a high level as reported by Sicuteri *et al.* (1961) while Curzon, Theaker, and Phillips (1966) found a correlation between high 5HIAA excretion and migraine attacks but in only two out of nine subjects studied.

Increased urinary 5HIAA is probably due to breakdown of abnormally large amounts of 5HT released from sites in intestine, brain, blood platelets, etc., where it is unavailable to the enzyme monoamine oxidase required for its conversion to 5HIAA. A fall in plasma 5HT has been reported during migraine attacks (Curran *et al.*, 1965; Anthony, Hinterberger, and Lance, 1967). The mechanism by which this occurs may be similar to that by which reserpine causes release of 5HT from platelets (Hinterberger, Anthony, and Vagholkar, 1968). It is also known that reserpine may precipitate migraine attacks (Kimball and Friedman, 1961).

Spontaneous migraine is not easy to study biochemically, as the frequency of attacks is of only limited predictability and may decrease when patients are hospitalized and subjected to the attention necessary for biochemical investigation. It has been suggested, therefore, that reserpine induced attacks could be more conveniently studied than spontaneous attacks (Curzon, 1967). The relevance of such study to spontaneous migraine is dependent upon the degree of similarity of the reserpine headache symptoms and of the associated biochemical changes to those occurring in spontaneous migraine. Therefore, the relationship of reserpine induced migraine to urine 5HIAA and blood 5HT changes was studied. High urinary excretion of 3-methoxy-4-hydroxy mandelic acid (VMA) a terminal metabolite of noradrenaline and adrenaline, has been reported in spontaneous migraine by some investigators (Sicuteri, 1963; Curran *et al.*, 1965) but has not been found by others (Curzon *et al.*, 1966). The relationship of urinary VMA changes after reserpine headache was therefore also investigated.

MATERIALS AND METHODS

SUBJECTS Patients were female volunteers selected from the headache clinics at the Elizabeth Garrett Anderson Hospital, Euston, and the Princess Alexandra Hospital, Harlow, but all were investigated at the former hospital. Most described characteristic prodromal symptoms and were diagnosed as having classical migraine. A few patients had no prodromal symptoms and, therefore, were classified as having non-classical migraine. They were aged between 22 and 62 and had suffered from recurrent headaches for at least a year. None had signs of organic neurological, vascular, or gastrointestinal disease. Patients remained in bed during investigation and were asked to keep off drugs, apart from simple analgesics, for two days before admission and during study. The normal hospital diet was used except that the following foods, which contain 5HIAA, VMA, and/or their precursors in considerable amount or which might alter amine metabolism were excluded from the diet: banana, tomato, pineapple, walnuts, apricots, alcohol. All patients were non-smokers except nos. 1, 5, and 16, who smoked 15, one, and 20 cigarettes/day respectively.

Reserpine (Ciba) 2·5 mg or placebo (water) was injected subcutaneously at 10 a.m. on the third day after admission to hospital. Patients 6, 7, and 8 were injected with placebo on the second day after admission and also with reserpine on the third day. A double blind design was used with all except these three subjects who all developed headaches after reserpine. Vascular side-effects of reserpine may well have given the observer clues concerning whether drug or placebo was given.

URINE COLLECTIONS Serial four hour urine specimens were collected into 10 ml. N hydrochloric acid and stored at 4°C for up to four days, after which volumes were measured and samples stored at −25°C until used for determinations.

METHODS 5HIAA, VMA, and creatinine were determined, using standard methods slightly modified as indicated by Curzon *et al.* (1966). 5HIAA and VMA excretions were expressed in terms of creatinine excretion, thus correcting for possible defects in urine collection and for variations in urine flow. Blood 5HT was determined as described by Ashcroft, Crawford, Binns, and MacDougall (1964) except that the lysed blood was saturated with coal gas before deproteinization (Rodnight, 1958).

RESULTS

CLINICAL RESULTS These are summarized in Table I. Of the 16 subjects to whom reserpine was given, nine had headache attacks commencing within six hours of the injection. The mean time of onset was 2·3 hours after injection and severe symptoms occurred within either the first or second four hour period after injection. Five of these subjects considered their headaches as typical. The other four subjects described unusual side-effects and attacks which were milder than usual. The subjects with headaches after reserpine were divisible into groups of five and four with severe and moderate symptoms respectively. Although six of these nine subjects usually suffered from classical migraine, only two described prodromal visual disturbances. Facial flushing was noted in the patients who developed headache after reserpine, but was noted to occur by only one patient in spontaneous attacks. The other subjects given reserpine described no headaches or very slight almost continuous headaches which were not exacerbated by the drug. Two of the seven subjects who did not develop headache within 12 hours after reserpine injection had an attack during the previous two days. Results, however, do not suggest that failure of reserpine to precipitate headache was related to this, as two of the nine subjects with headache after reserpine also had had attacks within the previous two days. These attacks may have been related to withdrawal of drugs. No abnormal signs except peripheral vascular dilatation were found on examination of patients after reserpine injection. The blood pressure was not significantly altered. Comparison of patients in whom reserpine induced headache with those in whom it did not failed to show any apparent clinical differences between them. Neither did they respond differently to drug therapy nor were they of significantly different weights or surface areas (Table I). It is of interest, however, that the only patients who considered their headaches to be improving (nos. 10 and 11) did not have headaches after reserpine.

TABLE I

CLINICAL FINDINGS

No.	*Age*	*Diagnosis*	*Time since last attack (days)*
Headache after reserpine			
*1	34	Non-classical	3
*3	33	Classical	5
*6	22	Classical	37
*8	32	Classical	3
*24	35	Classical	19
2	30	Classical	2
4	45	Non-classical	2
5	26	Classical	7
7	46	Non-classical	21
No headache attack after reserpine			
9	46	Classical	12
10	41	Classical	—
11	55	Classical	2
12	47	Non-classical	1
13	47	Classical	9
22	54	Non-classical	3
23	52	Classical	3
No headache attack after placebo			
14	23	Classical	2
15	52	Classical	—
16	35	Non-classical	13
17	45	Classical	3
18	26	Classical	40
19	47	Classical	1
20	62	Non-classical	4
21	38	Classical	3

*Headache after reserpine was severe in patient's estimation.

RELATIONSHIPS BETWEEN INDUCTION OF HEADACHE BY RESERPINE AND WEIGHT OR SURFACE AREA

	Subjects	*Weight (kg)*		*Surface area (m^2)*	
Reserpine	Headache (8)	62 ± 6	N.S.	1·67 ± 0·07	N.S.
	No headache (5)	62 ± 10		1·70 ± 0·16	

Numbers of subjects in parentheses.

BIOCHEMICAL RESULTS The level of sympathetic nervous activity or of 5HT turnover before reserpine injection might conceivably have some influence upon inductibility of headache after reserpine treatment. Table II shows 5HIAA/creatinine and VMA/

TABLE II

URINARY EXCRETION OF 5HIAA/CREATININE AND VMA/CREATININE BEFORE RESERPINE INJECTION

		5HIAA/creatinine (mg/g)	*VMA/creatinine (mg/g)*
Reserpine	Headache	3·30 ± 0·91 (8)	4·64 ± 1·02 (7)
	No headache	3·19 ± 1·69 (5)	4·79 ± 0·86 (5)
	Placebo	2·56 ± 1·12 (8)	4·33 ± 1·03 (8)
		No significant differences	No significant differences

Numbers of subjects in parentheses.

creatinine excretion in the four hour period before reserpine or placebo injection. There is no significant relationship between these values and headache precipitation, which thus appears independent of gross catecholamine or 5HT turnover before reserpine in so far as these are indicated by the VMA and 5HIAA results.

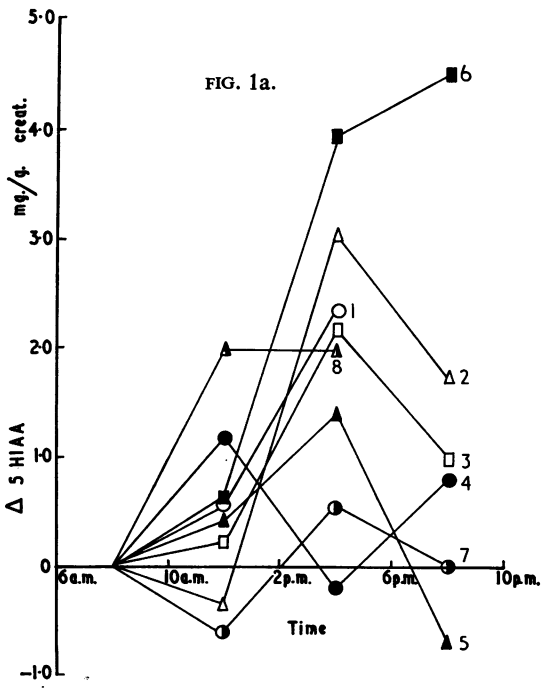
Effects of reserpine on 5HIAA excretion are shown in Figure 1. Subjects describing moderate or severe migrainous symptoms mostly showed increased excretion of 5HIAA/creatinine after injection. Subjects who did not have attacks after reserpine had less marked changes in 5HIAA/creatinine. The difference in 5HIAA/creatinine excretion of the groups is most marked in the period four to eight hours after reserpine injection. Figure 2 shows the relationship between age and the increase in 5HIAA/creatinine excretion in the period four to eight hours after reserpine injection over that in the four hour period before injection.

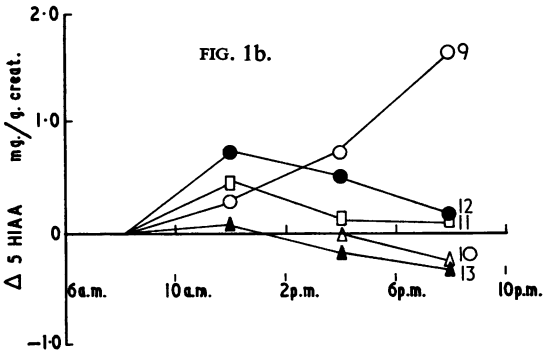
Table III shows statistical treatment of the results in Figures 1 and 2. There are a number of highly significant relationships. Subjects who had attacks after reserpine injection showed a significant increase in 5HIAA/creatinine when compared either with subjects who did not have attacks after reserpine or with subjects given placebo. There is also a significant correlation between increase of 5HIAA/creatinine excretion after reserpine and age, smaller increases being observed in older subjects. This cannot be explained by differences in weight or body form, no correlation between these parameters and age being apparent. Two of the reserpine subjects (nos. 10 and 11) had had a hysterectomy, while the rest had not reached the menopause.

The above changes of 5HIAA/creatinine appear to be due to changes in formation of 5HIAA and are not merely a reflection of changes in creatinine output, which were negligible (Table III).

Results in Table IV show that 5HIAA/creatinine excretion increases after reserpine injection when compared with that excreted by the same subjects in the same four hour period on a previous day when placebo was given. This indicates that rises in 5HIAA output after reserpine are associated with reserpine administration and are not merely due to abnormal diurnal variations of 5HIAA.

The effect of reserpine on VMA/creatinine excretion and the relationship between age and increase





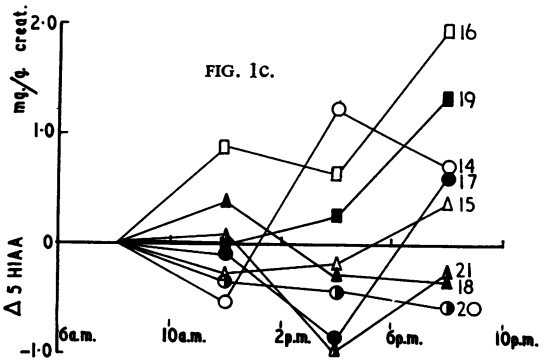


FIG. 1. *Effect of 2·5 mg reserpine on urinary excretion of 5HIAA by migrainous subjects: (a) headache induced; (b) no headache; (c) placebo. Drug or placebo was injected subcutaneously at 10 a.m. Results are expressed as increases of excretion of 5HIAA/creatinine in four hour periods over that in the four hour period before injection.*

TABLE III

RELATIONSHIP BETWEEN Δ5HIAA/CREATININE AND ΔVMA/CREATININE EXCRETION AFTER RESERPINE INJECTION AND HEADACHE INDUCTI

	Subjects	Age (yr)		Increases of excretion in period 4–8 hr after injection over that in period 4 hr before injectic: Δ5HIAA/creatinine (mg/g)		ΔVMA/creatinine (mg/g)	
Reserpine	Headache	33·5 ± 8·4 (9)	P<0·01	1·92 ± 1·33 (8)	P = 0·05–0·02	3·17 ± 1·74 (7)	P = 0·05–0·02
	No headache	47·2 ± 5·0 (7)		0·25 ± 0·13 (5)		0·94 ± 1·06 (5)	
	All subjects	38·8 ± 9·9 (16)	P = 0·02	1·28 ± 1·34 (13)	P<0·01	2·21 ± 1·81 (12)	P<0·(
			N.S.		P<0·02		P = 0·05–0·02
Placebo		41·0 ± 13·1 (8)		−0·08 ± 0·76 (8)		0·46 ± 0·95 (8)	

CREATININE EXCRETION BEFORE AND AFTER RESERPINE INJECTION

	Subjects	Creatinine excretion (mg): 4 hr period before injection	4–8 hr after injection
Reserpine	Headache (8)	151 ± 37	160 ± 67
	No headache (5)	174 ± 54	172 ± 79
	All subjects (13)	161 ± 42	163 ± 68
Placebo (8)		171 ± 90	164 ± 67

None of these values are significantly different.

RELATIONSHIPS BETWEEN △5HIAA/CREATININE AND △VMA/CREATININE EXCRETION AND AGE

Correlation coefficients y = a + bx (x = age)

y	Subjects	b	a	r	P
Δ5HIAA/creatinine (13)	Reserpine	−0·1158	6·770	−0·68	<0·001
ΔVMA/creatinine (12)	Reserpine	−0·1202	7·842	−0·67	<0·02
Δ5HIAA/creatinine (8)	Placebo				N.S.
ΔVMA/creatinine (8)	Placebo				N.S.

Numbers of subjects in parentheses. r = correlation coefficient and *P* the probability of this occurring by chance.

in VMA/creatinine are shown in Figs. 3 and 4 respectively. Relationships with headache and age are qualitatively similar to those found for 5HIAA and are statistically significant (Table II). 5HIAA/creatine changes and VMA/creatinine changes after reserpine are approximately in proportion to each other (Fig. 5).

Blood 5HT Usually blood 5HT fell after reserpine injection, very low or undetectable levels being reached within 24 hours (Table V). However, blood 5HT rose in some subjects during the first two hours after injection, perhaps due to normal variation of blood 5HT before the reserpine action was

TABLE IV

INCREASE OF 5HIAA/CREATININE EXCRETION AFTER RESERPINE INJECTION

No.	Increase of 5HIAA/creatinine (mg/g†): 10 a.m.–2 p.m.	2–6 p.m.	6–10 p.m.
8	1·21	3·04	—
3*	0·25	0·76	1·14
6	0·72	4·18	5·02
2*	0·44	1·87	1·05
7	0·58	0·68	0·67

2·5 mg reserpine was injected subcutaneously at 10 a.m. Headache attacks were precipitated in all cases.

*These urines were collected after a second reserpine injection one year after the investigation indicated in Fig. 1.

†Increase over the excretion during same period on previous day when placebo was given at 10 a.m.

TABLE V

RELATIONSHIP OF HEADACHE SYMPTOMS TO BLOOD 5HT CHANGES AFTER RESERPINE INJECTION

No.	Headache	Blood 5HT (μg/ml.)
1*	Severe Started 1.30 p.m.	0·122 (10 a.m.); 0·084 (10.45 a.m.) 0·061 (12.15 a.m.); 0·043 (1.45 p.m.) 0·028 (6.30 p.m.)
5	Moderate Prodromal 10.15 a.m. Started 11 a.m., worse 2.30 p.m.	0·155 (10 a.m.); 0.137 (10.30 a.m.) 0·130 (11.15 a.m.); not detectable (10 a.m. next day)
6	Severe at 11 a.m.	0·113 (10 a.m.); 0·113 (10.30 a.m.) 0·142 (noon); 0·135 (1.30 p.m.) not detectable (10 a.m. next day)
7	Moderate Started 1 p.m.	0·073 (10 a.m.); 0·085 (11.30 a.m.) 0·065 (1.00 p.m.); 0·057 (2.00 p.m.) 0·133 (4.45 p.m.)
8	Severe Started 11.30 a.m.	0·140 (10 a.m.); 0·137 (11 a.m.) 0·120 (11.30 a.m.); 0·116 (12.30 p.m.) 0·088 (1.30 p.m.); 0·080 (3.30 p.m.) 0·046 (5.30 p.m.)
22	None	0·150 (10 a.m.); 0·138 (10.30 a.m.) 0·061 (2.30 p.m.); not detectable (10 a.m. next day)
23	None	0·162 (10 a.m.); 0·202 (11 a.m.) 0·172 (noon); 0·160 (1 p.m.) 0·165 (10 a.m. next day)

*One year after investigation indicated in Fig. 1.

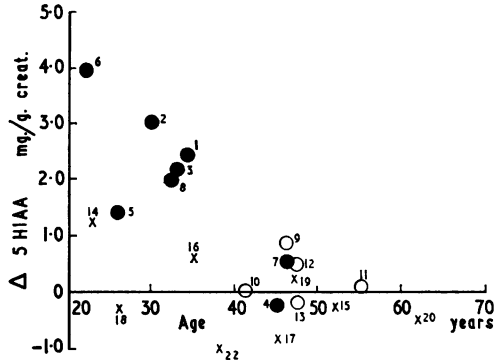


FIG. 2. *Relationship between age and urinary excretion of 5HIAA after reserpine injection. Results are expressed as increases of excretion of 5HIAA/creatinine in the period four to eight hours after injection over that in the four hour period before injection.* ●, *headache induced;* ○, *no headache;* ×, *placebo.*

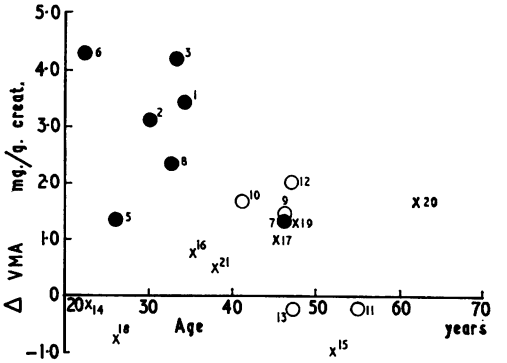


FIG. 4. *Relationship between age and urinary excretion of VMA after reserpine injection. Conditions and symbols as Fig. 2.*

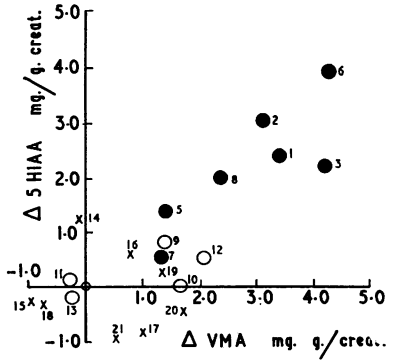


FIG. 5. *Relationship between changes in urinary excretion of 5HIAA and VMA after reserpine injection. Conditions and symbols as Fig. 2.*

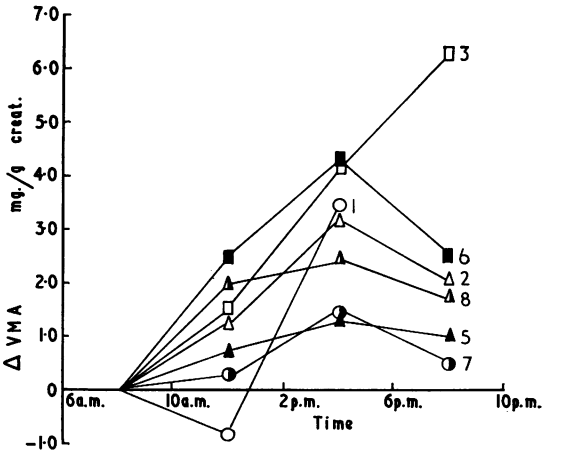
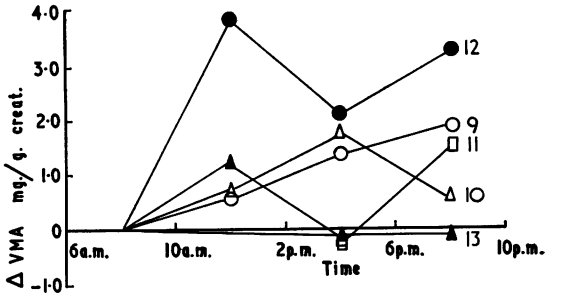


FIG. 3a.



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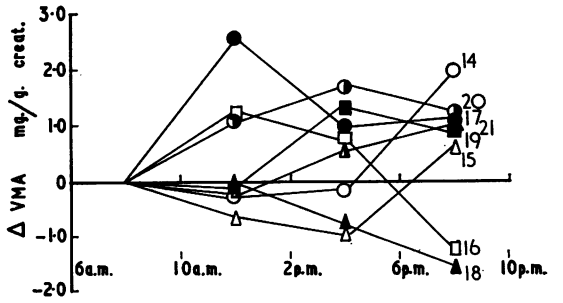

FIG. 3c.

FIG. 3. *Effect of reserpine on urinary excretion of VMA Conditions as Fig. 1: (a) headache induced; (b) no headache; (c) placebo.*

manifest. Considerable diurnal variations of plasma 5HT were found by Curran *et al.* (1965). The time course of headache symptoms is not clearly associated with that of the fall of blood 5HT. Thus symptoms first appeared in subjects 5 and 8 and were definite in subjects 6 and 7 before any marked decline in blood 5HT. However, well-defined urinary 5HIAA increases occurred in subjects 5, 6, and 8, that of subject 6 being larger than that of any other subject studied and associated with a particularly severe and prolonged headache. Table V includes results on two subjects who did not have headaches after reserpine injection. While the blood 5HT content of one of these (no. 22) eventually declined comparably with that of the subjects who had headaches, there was no evidence of a decline in the blood of the other subject (no. 23). Urines of these two subjects were not collected for 5HIAA and VMA determinations.

DISCUSSION

Migraine attacks occurred within six hours of injection of 2·5 mg reserpine subcutaneously in nine out of 16 female migrainous subjects. None of the residual seven subjects had an attack within the next six hours. Kimball and Friedman (1961) and Anthony *et al.* (1967) reported attacks after 2·5 mg reserpine in six out of six and nine out of 10 subjects respectively. These differences are presumably related to differences in experimental design and in selection of patients. Also age may be important, as our findings suggest that older subjects are more resistant to reserpine.

Reserpine induced headaches showed similarities to spontaneous migraine headache, being almost always one sided and lasting for a number of hours. Prodromal visual symptoms, however, were rare. Vasodilatation was more prominent in reserpine induced attacks, facial flushing invariably being noted. This was previously observed by Kimball and Friedman (1961) who point out that reserpine headache cannot simply be explained by vasodilatation as there was no consistent correlation between the intensity of these two factors and also other substances did not cause headache, although they resulted in vasodilatation.

Although reserpine has been known for over a decade to cause increased urinary excretion of amine metabolites, relatively little quantitative information is available. Todrick, Dick, and Tait (1958) gave 5 mg reserpine intramuscularly to male patients in an admission ward of a mental hospital and found increases in urinary 5HIAA/creatinine levels comparable with those in our study, although maximal effects in general appeared sooner and elevated levels persisted longer. As in our study, 5HIAA excretion was significantly affected in only about half of the subjects. McDonald and Weise (1962) gave 2·5 mg reserpine intramuscularly to normal male subjects between 18 and 24 years old. In agreement with our findings, the greatest increase in urinary VMA/creatinine was in the second four hour sample after injection. The mean increase in excretion above that after placebo injection was 1·92 mg VMA/g creatinine, which is comparable with that by the younger subjects in our study (Fig. 4). Thus, while comparisons do not permit definite conclusions, they do not suggest that amine stores of migrainous subjects are abnormally sensitive to the releasing action of reserpine. On the other hand, work by Campus, Fabris, Rappelli, Gastaldi, Gai, and Nattero (1967) suggests that an abnormal release mechanism may exist. They report that glyceryl trinitrate had no effect on 5HIAA excretion by normal subjects and did not cause headache but resulted in increased 5HIAA and VMA excretion and precipitated attacks in subjects suffering from vascular headache.

As a group, our patients in whom reserpine precipitated a migraine attack also had a markedly increased excretion of 5HIAA/creatinine and VMA/creatinine after reserpine injection, while those in whom an attack was not precipitated did not have a significantly increased excretion of these metabolites. This suggests that amine release may play an essential role in the development of reserpine headache, while the absence (Kimball and Friedman, 1961) or mildness (Anthony *et al.*, 1967) of headache in control subjects after reserpine injection indicates that abnormal sensitivity to amine changes is also involved.

In earlier work (Curzon *et al.*, 1966) high 5HIAA excretion by two subjects was concurrent with or preceded the severe part of spontaneous attacks and VMA did not rise. However, in reserpine induced attacks, both 5HIAA and VMA excretion rose but these changes and also a fall of blood 5HT often occurred later than the onset of severe symptoms.

A striking finding was that patients who had headaches after reserpine were significantly younger than those who did not. Also the effect of reserpine on the excretion of 5HIAA/creatinine or VMA/creatinine was in general more marked in younger patients. Winsor (1954) noted that the hypotensive effect of reserpine is more marked in middle-aged than in elderly patients. Also Hecht (1960) found that the behavioural effects of reserpine on 6-month-old rats was more pronounced than that on 12-month-old rats. Furthermore, Kulkarni and Shideman (1966) found that the depletion of rat brain catecholamines by reserpine was in the order infant >

weanling > adult. One interpretation of these observations is that releasability of amines from body stores in response to certain agents may decrease with increasing age. The frequent tendency of migraine to decrease or disappear in later life might be related to a similar decreased releasability by physiologically occurring substances. However, it would be incautious at present to over-stress this interpretation. The subjects studied were self-selected by their willingness to spend a number of days under investigation. Older women, having in general less pressing family responsibilities, might accept hospitalization more readily and therefore the older subjects studied might as a group not be as ill as the younger ones. Such a difference was not apparent, but if present though unrecognized the results might point to a smaller release of amines by reserpine in less severely ill patients rather than a relationship with age.

It would be of interest to determine whether the apparent relationship between age and increased 5HIAA and VMA excretion after reserpine injection holds for non-migrainous subjects and, if so, whether it is in fact due to differences in releasability of 5HT and catecholamines by reserpine, or to differences in the metabolism of these substances after release, or even to differences in the metabolism of reserpine itself.

SUMMARY

Headache attacks were induced in nine out of 16 female migrainous patients by injection of 2·5 mg reserpine intramuscularly. Attacks induced by reserpine were usually similar to spontaneous ones, being prolonged and one-sided, but prodromal signs were less frequent and vascular changes were more prominent than in spontaneous attacks. Subjects in whom reserpine induced attacks showed significant increases in urinary 5HIAA/creatinine and VMA/creatinine compared with subjects who did not have attacks. The latter subjects were significantly older than those who had attacks and there was a significant negative correlation between age and the increases of 5HIAA/creatinine and VMA/creatinine. There was no clear relationship between the time course of the fall of blood 5HT after reserpine and the appearance of headache symptoms.

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