Cerebrospinal Fluid 5-Hydroxyindoleacetic Acid Level in Migrainous Patients During Spontaneous Attacks, During Headache-Free Periods and Following Treatment with L-Tryptophan.

An involvement of 5-hydroxytryptamine (5-HT) in migraine is now accepted: an elevated urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA) and of 5-HT with a significant fall in plasma 5-HT has been reported[1-7].

The clinical features of migraine attacks actually suggest an important involvement of the central nervous system, and 5-HT seems to play an important role as modulator in some nervous functions typically affected in the migraine, such as the emotional and vegetative ones[8]. A sudden decrease of brain 5-HT has recently been suggested in migraine patients during attacks[8]; nevertheless 2 reports only concern the cerebrospinal fluid (CSF) 5-HT level in these subjects[9,10] and 5-HIAA has only recently been determined[11].

In the experiments here reported, samples of CSF taken by lumbar puncture from migraine patients during a spontaneous attack and in headache-free periods, and from patients without migraine taken as controls, were examined for 5-HIAA content; the changes in CSF 5-HIAA level following 10 days tryptophan administration and the clinical effects are also discussed.

All the patients who volunteered, after a careful explanation of the procedures involved, were kept in bed and refrained from drugs and food which are known to contain amines or substances which might alter the metabolism of the amines. 5-HIAA was determined according to the method of ASCHCROFT and SHARMAN[12], and the results were statistically evaluated by standard procedures (Student's *t*-test).

No difference was noted between the migraine patients in headache-free periods and the controls; the values recorded during spontaneous attacks appear to be lower than the preceding values, but this difference does not attain statistical significance; moreover all values recorded are included within the normal range (20–40 ng/ml; Table).

Following 10 days L-tryptophan administration (3 g, 3 times daily, per os), supplemented by pyridoxine (300 mg daily, i.m.) and ascorbic acid (1 g daily, i.v.), a significant increase in the CSF 5-HIAA content was noted, in all the 5 patients studied (Figure). This rise was comparable to what we have observed in 2 patients, taken as controls (Figure): a similar increase in CSF 5-HIAA was recorded by ECCLESTON[13] in different neurological patients after a single large oral dose of the amino acid and by DUNNER[14] in depressed subjects treated with L-tryptophan in the same doses as we used. Moreover, during the treatment 3 patients did not feel headache, 1 patient noted a decrease in the frequency and severity of the attacks, while the last patient did not show any improvement.

Conclusions. Our results are not in keeping with those of KANGASNIEMI[11], who noted an increase, though not significant, of CSF 5-HIAA during migraine attacks; nevertheless the small and not statistically significant decrease that we have recorded, gives no certain clues to the hypothesis of a sudden deficiency of brain 5-HT during migraine attacks.

The presence of a permanent disorder of brain 5-HT turnover seems quite improbable: in fact the migraine patients that we have studied seem able to utilize L-tryptophan to form 5-HT and to deaminate 5-HT to form 5-HIAA.

Nevertheless, prolonged L-tryptophan treatment has been found to prevent migraine attacks in 3 out of 5 patients. As reported by KIMBALL et al.[15] and ANTHONY

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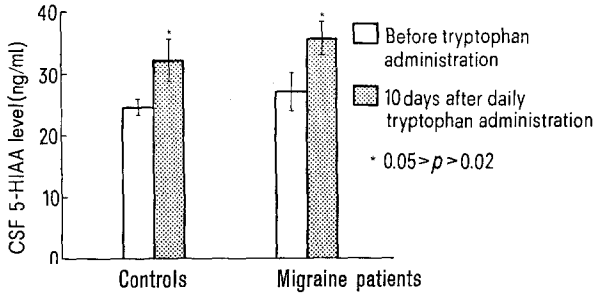
Sex, age, 5-hydroxyindoleaceticacid (5-HIAA) levels in lumbar cerebrospinal fluid in 5 migraine patients during the attacks and in headache-free periods

Case	Sex	Age	5-HIAA levels in headache-free periods (ng/ml)	5-HIAA levels during attacks (ng/ml)	5-HIAA levels in 5 controls (ng/ml)
1 S.E.	♀	37	30.1	20.0	
2 B.E.	♀	44	35,2	20.8	
3 A.M.	♀	31	32.4	26.7	21.9↔40.0
4 P.R.	♀	38	30.5	28.2	
5 G.A.	♀	22	28.6	30.4	
Means ± S.E.			31.2 ± 1.2	25.2 ± 2.0	31.1 ± 3.1

The values reported on the right are referred to 5 subjects used as controls.

et al.[4], both spontaneous and reserpine-induced migraine attacks are relieved by the i.v. injection of 5-HT or 5-hydroxytryptophan; moreover the monoamino-oxidase inhibitors are known to alleviate headache. These effects, in our opinion, could not be merely explained on the basis of tryptophan ability to increase the synthesis of brain 5-HT.



Cerebrospinal fluid levels of 5-hydroxyindoleacetic acid (5-HIAA) immediately before and following 10 days of L-tryptophan administration (see text) in 5 migraine patients and in 2 neurological patients, taken as controls.

The possibility remains that 5-HT involvement migh occur only in some restricted areas of the brain; in that case fine CSF biochemical changes would be too difficult to evaluate.

Riassunto. La concentrazione di acido 5-idrossindolacetico nel liquor lombare di pazienti emicranici diminuisce lievemente e non significativamente durante l'attacco, mentre, in periodo intercritico, non è diversa da quella osservata nei soggetti normali. La somministrazione di L-triptofano porta costantemente ad un incremento dei livelli di acido 5-idrossindolacetico nel liquor lombare di soggetti emicranici, oltre ad esercitare un'azione preventiva degli accessi di cefalea.

M. Poloni, G. Nappi, A. Arrigo and F. Savoldi

Clinica delle Malattie Nervose e Mentali dell'Università, Via Palestro 3, I-27100 Pavia (Italy), 1 October 1973.

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Urinary Excretion of Methylated Purines Following Inhalation of Dimethyl Sulphate

Dimethyl sulphate (DMS) is a widely used industrial and laboratory methylating agent. It has been shown to be carcinogenic in laboratory animals[1-3]. Methylation of nucleic acids of several organs has been detected in rats given i.v. injection of radioactively labelled DMS[4]. The principal site of methylation in nucleic acids by methylating agents is *N*-7 of guanine, but a number of sites, including the phosphodiester group, with less reactivity have been detected (cf. refs. [5,6]). The alkylations of nucleic acids which result in hereditary changes are not fully known, but methylation at O^6 in guanine seems to affect the coding property[7], whereas methylation at *N*-7 in guanine does not[8].

7-Methylguanine (7/MeGua) formed by methylation in DNA is liberated by hydrolysis[9,10] and in RNA by metabolic turnover[11]. An exogenous dose of 7MeGua is mainly excreted unchanged in the urine within a short time[12]. Urinary excretion of labelled 7MeGua has been used as an indication of methylation of nucleic acids in mammals exposed to labelled methylating agents[13-16].

Quantitative determinations of the urinary 7MeGua in relation to the administered dose of labelled methylating agents may thus give information about the overall extent of alkylation of nucleic acid constituents in the whole body. Parallel to such a study with the insecticide dimethyl dichlorovinyl phosphate (dichlorvos)[16], we have performed inhalation tests with DMS in male NMRI mice.

DMS labelled with ^3H with a specific activity of 150 mCi/mmole (Radiochemical Centre, Amersham) was used. 4 animals were exposed in each of the 2 tests (cf. Table) in a 6 l glass flask. In experiment 2 the labelled DMS was applied to a wad of glass fibres hanging in the flask, but for the high dose exposure (experiment 1) the DMS was applied to the wad in a glass tubing, connected with the flask, through which a slow stream of air passed; the latter arrangement made it possible to keep the animals under exposure for a longer time. The air concentration of DMS was monitored during the exposures by counting the radioactivity of air samples drawn from the flask. In experiment 1 the air concentration was, in addition, determined by reacting air samples with 4-(p-nitrobenzyl)-pyridine[17]; both types of analysis gave the same result. The maximum DMS concentrations in both experiments were about 4 times the average concentration which is given in the Table. The total exposure given in the Table have been calculated by assuming that the mice had a minute volume of 24 ml; this is obviously an underestimate in experiment 2 as the recovered urinary excretion is slightly larger.

After exposure the animals were placed in a metabolic cage with access to water and the urine was collected

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