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Short Communication

Serotonin, Noradrenaline, Dopamine Metabolites in Transcendental Meditation-Technique*

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With 1 Figure

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Summary

The highly significant increase of 5-HIAA (5-hydroxyindole-3-acetic acid) in Transcendental Meditation technique suggests systemic serotonin as "rest and fulfillment hormone" of deactivation-relaxation.

Furthermore 5-HT (5-hydroxytryptamine, serotonin) is considered to to be the EC-cell (enterochromaffine-cell) hormone requested by *Fujita* and *Kobayashi* and its role for EEG synchronisation via area postrema chemoreceptor as anti arousal agent is being discussed.

The significant decrease of the catecholamine metabolite VMA (vanillic-mandelic acid) in meditators, that is associated with a reciprocal increase of 5-HIAA supports as a feedback necessity the "rest and fulfillment response" versus "fight and flight".

As the adreno medullary tissue serves for hormonal reinforcement of orthosympathetic activity, the Enterochromaffine Cell System (having taken the form of distinct organs in some species as octopus and discoglossus) is suggested to serve via serotonin for humoral reinforcement of parasympathetic activity in deep relaxation.

Introduction

Transcendental Meditation (TM-technique) by *Maharishi Mahesh Yogi* (1966) is a mental relaxation and maturation technique as compared to physical relaxation techniques (Hatha-Yoga, Progressive

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Relaxation by *Jacobson*, Autogenic Training by *Schultz*). TM-technique improves and normalizes the emotional state, improves field independence, the ability to focus attention, reaction time and mind-body coordination without drugs.

Presently TM is practiced by over one million people according to SIMS organization statistics. This number and the spreading use in sports, government support in education and social rehabilitation (*Shafii et al.*, 1974; *Benson*, 1972) justify the investigation into the clinical effect.

The present study is an initial investigation of the effects of TM-technique on biogenic amines metabolites.

Material and Methods

A. TM-Program Participants and Clinical Staff

This investigation was carried out with 11 healthy practitioners (4 female, 7 male) of TM-technique, and the data compared to those obtained from the controls, 13 healthy subjects of the clinical staff, chosen to approximate the age and sex distribution of the experimental group and to account for ultradian rhythm. TM-experimental subjects were regular Meditators obtained through the Students International Meditation Society, Austria. The selection of the meditators was essentially random. The age distribution of the TM-practitioners ranged from 19 to 61 years, the average length of regular TM-practice was 29 months ± 11 ranging from 14 to 54 months. As a routine the technique is practiced twice daily for 20 min, morning and evening.

B. Sample Taking

Of the 11 meditators samples of 2 hour urine were taken 2 hours before and 2 hours after the start of the 30 min TM-practice in the group (3 p.m. to 5 p.m. and 5 p.m.—7 p.m.).

The controls practicing no form of relaxation and the TM-practitioners except for their 30 min of meditation were subjected on separate days to the same condition of light activity (conversation and occasional walks) during the 4 hours of the experiment. After collection the pH-value of the urine was immediately adjusted to 2—2.5 with the aid of 6 n hydrochloric acid. The urine was examined for indoleacetic acid, 5-hydroxyindole-3-acetic acid, homovanillic acid, and vanillic-mandelic acid. Urine that could not be analyzed immediately was frozen at —32 °C and analyzed at the latest 3 days after.

C. Influence of Circadian Rhythm and Diet

The circadian rhythm of 5-hydroxyindole-3-acetic acid, homovanillic acid, vanillic acid, and vanillic-mandelic acid was examined by *Riederer et al.* (1974) in urine from a healthy group of subjects divided into four fractions according to time of day. The fractions for the intervals from 8 a.m. to

2 p.m.; 2 p.m. to 8 p.m.; 8 p.m. to 2 a.m.; 2 a.m. to 8 a.m. showed a maximum of vanillic-mandelic acid and homovanillic acid during the waking state (8 a.m.—2 p.m.; 2 p.m.—8 p.m.), and a significant decrease during the sleep state (8 a.m.—2 p.m.; 2 p.m.—8 p.m.). During the day, there was no significant alteration shown in the concentration of 5-hydroxy-indole-3-acetic acid. From these investigations, the conclusions could be made that significant alterations of the metabolite concentration in the urine do not take place during a period of 2 to 4 hours.

To test this hypothesis, urine from 7 healthy subjects was collected at the same time of day, under the same time conditions previously described. The result showed, that in fact, no circadian rhythmic influence on the concentration of homovanillic acid, vanillic-mandelic acid, indoleacetic acid, and 5-hydroxyindole-3-acetic acid, was evident during 3 hours (*Riederer et al.*, 1975). Dietary influence on the substances mentioned have been described (see *Riederer et al.*, 1974, 1975). It was seen to that no interfering foods were consumed by any of the persons studied.

D. Biochemical Methods

In principle thinlayer- and gas chromatography methods have been applied.

In brief, aliquot amounts of the urine samples were centrifuged, and then shaken out several times with the same amount of peroxide-free diethyl ether each time (E. Merck AG., Darmstadt, FRG, p.a.). The diethyl ether fractions were collected and dried over waterfree sodium sulfate (E. Merck AG., Darmstadt, FRG, p.a.). The ether fractions dried in this manner were then distilled completely dry at 40 °C on a Rotavapor. The device was ventilated with pre-dried pure nitrogen (AGA-Vienna, p.a.) and the sediment was put into flasks as fast as possible in 2 ml of a mixture of ethyl acetate-methanol (8 : 2). The thin-layer chromatography, the demonstration, and the quantitative establishment of the individual metabolites were performed in the manner described by *Riederer et al.* (1974).

The results were scrutinized in a random test with the aid of gas chromatography. The method from *Sandler* (1973) was employed to establish homovanillic acid and vanillic-mandelic acid. Homovanillic acid and vanillic-mandelic acid were isolated from human urine by ethylacetate extraction. Two-hour urine collections were made. The urines were titrated to a pH-value of 2 during collection and stored at —32 °C. After evaporation to dryness the residue was diluted with 5 ml ethylacetate. 0.1 ml were evaporated by freeze drying in a 1 ml Reacti-Vial (Pierce Chemical Co., Rockford, Ill., U.S.A.). Derivatization of HVA and VMA were carried out adding 0.5 ml ethanolic HCl. After 30 min at room temperature 1.4 ml abs. ethanol (E. Merck AG., Darmstadt, FRG, p.a.) were added. A 50 μl aliquot was freeze-dried; 20 μl acetonitrile and 100 pentafluoropropionic anhydride were added. Reaction was carried out at 65 °C for 40 min in sealed Reacti-Vials. The derivatives of HVA and VMA were reconstituted in dry ethyl-acetate.

GLC analysis was carried out on a Perkin Elmer model 3920 instrument using electron capture detection. Separation was achieved on a 12 ft. glass column packed with 10 % SE-54 on Chromosorb W-HP (80—100 mesh). The column oven temperature was 200 °C. The injection block was maintained at 200 °C and the EC-dedector at 280 °C.

Results

The data in figure 1 demonstrate for the controls, that the urine concentration of VMA (main noradrenaline metabolite), HVA (main dopamine metabolite). 5-HIAA (main serotonin metabolite) and IAA (tryptamine metabolite) of the 2 hours periods 3 p.m.—5 p.m. (A) and 5 p.m.—7 p.m. (B) are not significantly different.

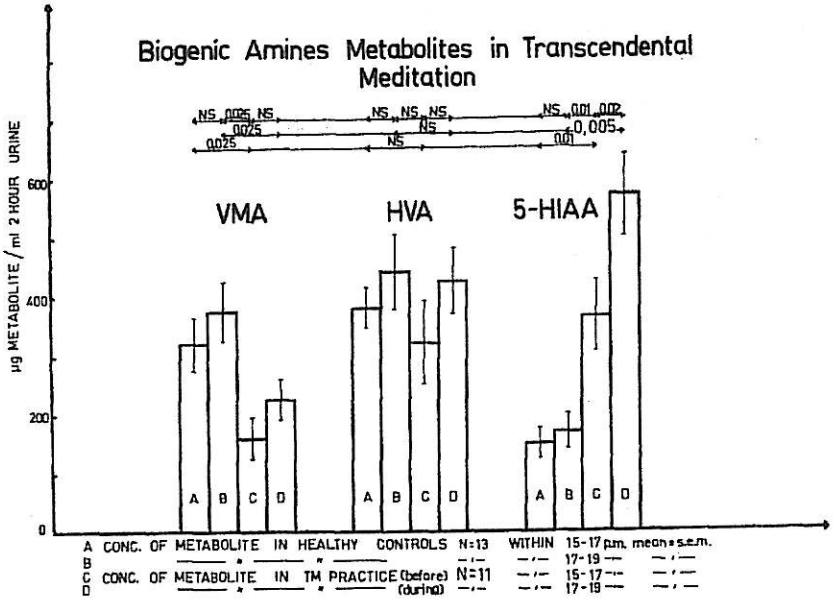

Fig. 1. t-Test for paired values between C/D for 5-HIAA were significant at the $p < 0.05$ level, those for VMA between A/D were significant at the $p < 0.02$ level

In TM-practice (comparing the 3 p.m.—5 p.m. premeditation period (C) to the 5 p.m.—7 p.m. TM and postmeditation period (D), that includes 30 min of TM-practice), the meditators, serving as their own controls, showed a significant increase of 5-HIAA ($p < 0.02$).

This allows for the conclusion that TM-technique has an effect of increasing serotonin metabolism. The increase of the other neurotransmitter metabolites does not become significant.

TM-practitioners 7—9 hours after their regular morning meditation, showed in their 2 hour urine metabolite sample (C) taken before the 5 p.m.—7 p.m. afternoon meditation period (D), a significantly lower VMA concentration (as compared to the controls) and a higher 5-HIAA concentration significant at the $p < 0.01$ level, rising to $p < 0.005$ after TM. These data allow for the conclusion that the meditators exhibit a lower level of activation (*Frankenhaeuser*, 1969), less stress and strain and have a lower adrenal hormonal level out of TM-practice periods also than our controls.

The elevated 5-HIAA conc. (C) indicates a sustained serotonin level well above control values in regular meditators during the day, rising with TM-practice (D).

It should be stated that in meditators compared to non-meditators a significant decrease in concentration of a main metabolite of the catecholamines noradrenaline and adrenaline, namely VMA, is associated with a reciprocal increase of the main metabolite of serotonin. This effect can be associated with the known effects of TM: synchronisation of EEG, decrease of muscle tone, decrease in anxiety etc. (*Banquet*, 1973; *Orme-Johnson* and *Farrow*, 1976).

The observed trend during daytime can be interpreted as lowered "basal activation". In meditators the ratio of the metabolites before and after TM followed a general logic and tended to a certain ratio (*Bujatti*, 1976).

Discussion

Referring to the data on the physiology of TM by *Wallace, Benson* and *Wilson* (1971), *Selye* (1975) writes: "TM's physiologic effects on metabolism, breathing, skin resistance, blood lactate, brain waves and the cardiovascular system are exactly opposite to those identified by medicine as being characteristic of the efforts to meet demands of stress."

The reduction of plasma cortisol during and after TM (*Jevning et al.*, 1975) and the significant reduction of VMA in this study on TM is further evidence for the above description and is connected with an increase in 5-HIAA in TM-practitioners.

The increase of the serotonin metabolite 5-HIAA while IAA (indole-3-acetic acid) remains more constant suggests the following conclusion:

A: Since 5-hydroxylation of L-tryptophan is the rate limiting step in 5-HT biosynthesis (see for review *Hamon et al.*, 1974) the long term increase in 5-HIAA production should be due to the stimulation of L-tryptophan turnover to 5-HTP in TM-practitioners.

L-tryptophan-5-hydroxylase which as capable of metabolizing

L-tryptophan into 5-HTP (5-hydroxytryptophan) has been localized in mammalian intestinal mucosa (*Porter et al.*, 1961).

The occurrence of serotonin in the enterochromaffine (EC) cells has been evidenced by *Ersparmer* and *Azero* (1952). Furthermore, the EC-cells of the enterochromaffine cell system in the gastro-intestinal mucosa are the main site of production and storage of 5-HT in mammals (*Ersparmer*, 1963).

B: After EC-cell stimulation by administration of hypertonic glucose in the gut lumen:

a) EC-cells responded by emiocytotic release of the basal granules (*Kobayashi* and *Fujita*, 1974).

b) Formaldehyde induced fluorescence (Falck-Hillarp Method) in the EC-cells of the human duodenal mucosa disappeared (*Tobe, Kimura* and *Fujiwara*, 1967),

c) an elevated blood serotonin level in the portal vein followed (*Johnson* and *Jesseph*, 1961; *Johnson, Sloop* and *Jesseph*, 1962),

d) leading to the conclusion: The EC or enterochromaffine cell, which represents the predominant element in the gut endocrine system can now be called a "safely endocrine cell", *Fujita* and *Kobayashi* (1974), *Osaka, Sasagawa* and *Fujita* (1974).

Feyrter (1938, 1953) established the morphological concept of the "diffuse endocrine epithelial organs". The work of the Japanese research-groups on the "gastro-entero-pancreatic endocrine system" provide evidence for its value. *Feyrter* concluded among many others since *Ciacco* (1906) an endocrine activity of the EC-cells, yet the question after the hormone, its function and the endocrine targets remained.

By lowering orthosympathetic vegetative tone in TM-technique, the observed increase in serotonin metabolism and consecutive urine 5-HIAA excretion are infered to be caused by basal granulated EC-cell stimulation plus secretion of 5-HT.

Such mechanism is well established for the basal granulated G-cell (*Uvnas*, 1942; *Pe Thein* and *Shofield*, 1959; *Hunski et al.*, 1971; *Matsuo, Seki* and *Kitamura*, 1974) that belongs to the same Gastro-Entero-Pancreatic endocrine system (GEP-system) as the EC-cell and the Amine Precursor Uptake and Decarboxylation series (APUD-series) as well, producing in this case the intestinal hormone gastrin (*Solcia* and *Sampietro*, 1965; *Busolati* and *Pearse*, 1970; *Mitschke*, 1971).

"It is an important fact that the amines in the APUD-cells are present in addition to polypeptide hormones and there seems to be no reason for the EC-cell being an exception to this point." (*Fujita* and *Kobayashi*, 1974)

So far the increase of 5-HIAA in the TM-practice is the first physiological-functional evidence for serotonin itself to be the presumptive main EC-cell hormone requested by *Fujita* and *Kobayashi.*

As the adreno medullary tissue serves for hormonal reinforcement of orthosympathetic activity (*von Euler,* 1963) the Enterochromaffine Cell System (having taken the form of distinct organs in some species as octopus and discoglossus) is suggested to serve via serotonin for humoral reinforcement of parasympathetic activity in "rest and fulfillment" of deep relaxation.

The classification of 5-HT activity:

1. Locally upon smooth muscle (*Sleisenger et al.,* 1959) as "tissue hormone" and

2. its powerful stimulant action on intestinal peristalsis (*Bülbring* and *Lin,* 1958; *Bülbring* and *Crema,* 1959; *Lee,* 1960) bloodflow in the gut wall and mucous secretion (*Menguy,* 1969; *Thorson,* 1958) as "intestinal hormone" can be suggested now. 5-HT according to *Ersparmer* (1963) acts further on

3. dilatation of the coronary vessels in the heart, the tone of venous, arterial and capillaric bloodvessels (*Oates et al.,* 1966, suggested bradykinin involvement); its effect on the pulmonary arterial tree, the placenta and possibly the kidney, the suggested metabolic activity concerning glycogenolysis (*Kursky,* 1974) as well as the effects on uterine muscle, all could be considered along this line, as "systemic RF-hormone" activity, of practical clinical and explicatory value.

4. The systemic "rest and fulfillment hormone" (RF-hormone) finally should act via area postrema chemoreceptor through the reticulo-solitario-reticular feedback system (*Koella* and *Czicman,* 1965; *Koella,* 1974) on, last not least, the "neurotransmitter serotonin" with its supporting role for EEG-synchronisation (*Gaillard* and *Bartholini,* 1974), the common finding of EEG research done on TM (*Wallace, Benson* and *Wilson,* 1971; *Banquet,* 1973; *Banquet et al.,* 1974; *Kobal,* 1975; *Krahne,* 1975).

5. 5-HT, that is held responsible for a bewildering multitude of central regulatory effects is suggested to account as "negentropyflow transmitter" (*Bujatti,* 1976) for them and the deactivation of the "rest and fulfillment response" observed in TM-technique centrally and peripherally antagonistic to the activation of the "entropyflow transmitter" noradrenaline (DA?) in "fight and flight".

The term "rest and fulfillment response" is defined (*Bujatti,* 1976) as "the homeostatic, self-organizing tendency of the living system, that is to meet all possible stressors in such a manner, as to maintain on increasingly complex levels of integration, while fluctuating, a

stable state of least possible activation and of maximum possible deactivation, an ultimately zeroentropy-state". This "rest and fulfillment response" (RF-response) is basic to and inclusive of the activation of "fight and flight" and "stress" reactions that do appear as antagonists but ultimately are its own synergistic phenomenon.

It should also be mentioned that in acupuncture an increase of 5-HIAA in the urine was demonstrated (*Riederer et al.*, 1975). Simultaneously an increase of slow alpha-activity is observable in acupuncture (*Birkmayer et al.*, 1976).

The increase of 5-HIAA concentration in a mental relaxation technique (TM) and in acupuncture of a peripheral point indicates a more general validity of the above mechanisms mediated by central and peripheral serotonin.

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