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SEROTONIN METABOLISM IN LIVER DISEASE *

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Serotonin, (5-hydroxytryptamine, 5-HT, enteramine) is widely distributed in animal tissues and has been shown to have marked pharmacologic effects upon the gastrointestinal tract and cardiovascular system (1-4). Indirect evidence suggests that serotonin may play an important role in cerebral function, but, as yet, no direct connection has been established between serotonin and cerebral disease (5). Previous reports (6) and personal observations have shown a low normal excretion of 5-hydroxyindoleacetic acid, the end product of serotonin metabolism, in liver disease. The precursor of the serotonin of brain is apparently 5-hydroxytryptophan. In view of these facts, the possibility that severe liver disease by, in some way, affecting the production of 5-hydroxytryptophan, might alter brain function, was investigated by the following series of experiments.¹

MATERIALS AND METHODS

Ten to 23 mg. of 5-hydroxy-DL-tryptophan (5-HTP) sterilized by dry heating at 100° for one hour and dissolved in 100 ml. of 0.85 per cent saline solution was given intravenously over a 30 minute period to four patients in severe hepatic coma, to three patients with abnormal electroencephalograms but not in hepatic coma, and to one normal individual. Electroencephalograms were recorded before, during and after infusion. Where possible, 24 hour urine specimens were collected in 6 hour fractions, just prior to, and immediately after, 5-HTP infusion, and analyzed for 5-hydroxyindoleacetic acid (5-HIAA) by the procedure of Udenfriend, Titus and Weissbach (8). Platelet 5-HT content was determined by the butanol extraction procedure of Udenfriend, Weissbach and Clark (9) just prior to and one, two, and three hours after 5-HTP infusion. Blood ammonia levels were determined by the method of Seligson and Seligson (10) as modified in this laboratory.²

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¹ A preliminary report (7) of this work has appeared.

² Mimeographed copies of the modification will be supplied upon request to Dr. Bessman.

RESULTS

The electroencephalograms of all patients with hepatic failure exhibited the usual diffuse slow activity. During infusion of 5-HTP, all four patients (Table I) showed a diminution of the slow activity and an increase of fast activity, representing a change in the record toward a more normal pattern. However, none of the patients developed a completely normal pattern. Figure 1 shows samples of tracings from Patient M. B. before and during infusion. These changes lasted for two

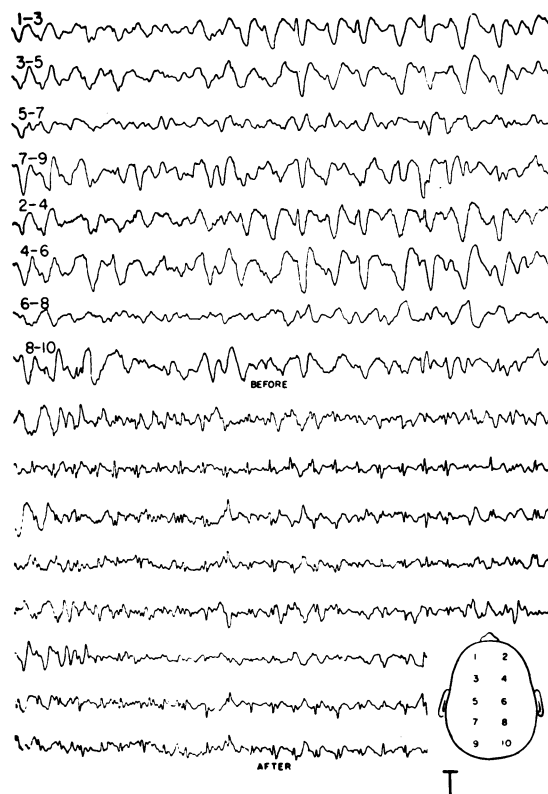


FIG. 1. ELECTROENCEPHALOGRAM BEFORE AND AFTER 5-HYDROXYTRYPTOPHAN (5-HTP) INFUSION. Calibration, 100 mV. and 1 second.

TABLE I
Clinical, metabolic and electroencephalographic response to 5-hydroxytryptophan (5-HTP) infusion

Patient, diagnosis	Av. 6 hr. urinary 5-HIAA* mg.	I.V. 5-HTP mg.	Recovery 5-HTP in 6 hrs. %	Blood ammonia† gamma/ml.	Blood 5-HT† gamma/ml.			Electroencephalogram change after I.V. 5-HTP	Clinical observations	Comment
					Control	1 hr.	2 hr. 3 hr.			
C. M. 12/6/56 Terminal hepatic coma	0.88	11.0	11/30 V, 1.55 A, 1.52 12/6 A, 0.99				Markedly diminished slow activity; prominent fast activity	None observed	Died 4 hours after 5-HTP	
V. O. 12/28/56 Severe hepatic coma	0.13	10.2	12/28 A, 1.82 V, 0.59 JB, 1.06	0.14	0.10	0.10	Increased fast activity	Abdominal cramps; no inc. in peristalsis	Died 4 hours after 5-HTP	
M. B. 1/17/57 Severe hepatic coma	1.37	10.9	1/17 A, 1.8 V, 1.1 JB, 1.7	0.18	0.11	0.19 0.12	Marked decrease in slow activity with increased frequency	Pulse inc. (16/min.) "Feel quiet and restful"		
M. C. 10/1/57 Mild hepatic coma	0.97	23.7	9/30 A, 1.44 V, 0.94	0.34	0.20	0.10	Moderate reduction of slow activity	Pulse inc. (24/min.)		
J. K. 12/23/57 Hodgkin's disease with mild hepatic coma	2.34 (per 24 hrs.)	40.4	12/24 Fem. A, 0.66 Fem. V, 0.88	0.03	0.03	0.02 0.02	Reduction in slow activity with increased fast activity	None observed	On Predisone, 15 mg. t.i.d.; KCl, 1 Gm. t.i.d.; 2 ml. Thiomerin® prior to 5-HTP	
P. H. 2/19/57 Subdural hematoma	0.61	10.6		Patients without hepatic insufficiency						
				0.12	0.20	0.11 0.20	No change		Pulse inc. (26/min.); inc. peristalsis	
A. F. 2/7/57 Chronic congestive heart failure	0.85	10.2		0.21	0.45	0.55 0.49	No change	Abdominal burning and cramps; inc. peristalsis; BP inc. (120/70 to 160/100)	Died 7 hours after 5-HTP	
W. C. 1/11/57 Normal	0.56	10.9		0.35	0.20	0.20 0.26	No change	"Tightness of stomach," "Can't get full breath," "Fullness in chest," "Feel cold." BP and pulse normal		
L. C. (W.F.—12) Epilepsy 3/28/57	0.37	12.1					No change	Inc. peristalsis; BP inc. (88/60 to 100/80)		

* Normal 24 hour urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA), 2 to 10 mg.

† Normal blood ammonia, less than 1 gamma per ml. arterial blood. Abbreviations are as follows: V, venous; A, arterial; JB, jugular bulb.

‡ Normal blood 5-hydroxytryptamine (serotonin), 0.1 to 0.3 gamma per ml.

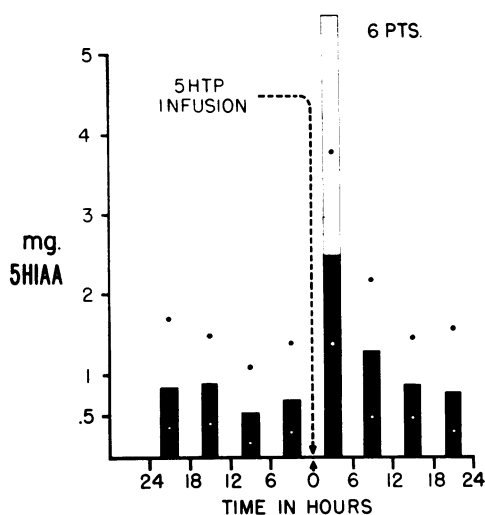


FIG. 2. INCREASED EXCRETION OF 5-HYDROXYINDOLE-ACETIC ACID (5-HIAA) FOLLOWING INTRAVENOUS 5-HYDROXYTRYPTOPHAN (5-HTP)

Dots represent high and low ranges. The bar is average excretion per six hour fractions.

hours in this patient and for about three hours in the remaining patients with hepatic insufficiency. In the three controls with abnormal electroencephalograms there was no change in the tracings on administration of 5-HTP, even though their tracings all showed markedly slowed activity bilaterally. In a normal individual, W. C., the administration of 5-HTP produced no changes in the electroencephalogram.

Figure 2 indicates the increased excretion of 5-HIAA following intravenously administered 5-HTP. Calculated on the assumption that only the l-isomer is metabolized, the average increased excretion in the first six hours represents a 46 per cent recovery of the administered dose of 5-HTP. If the excretion of the remaining 18 hours, in excess of the control period, is added to the first six hour excretion, a 52 per cent recovery is realized in 24 hours. The average 24 hour excretion of 5-HIAA was 3.1 mg. in the patients with hepatic coma and 2.4 mg. in the control patients. There was no significant difference in these values, which lie in the low normal range. In the case of Patient J. K., with liver failure secondary to extensive Hodgkin's disease involvement of the liver, spleen and retroperitoneal soft tissues, we had the opportunity to observe the effects of a diuretic on 5-HTP metabolism. Just

prior to the administration of 40.4 mg. of 5-HTP, 2 ml. of mercaptomerin sodium was administered inadvertently. The urine resulting from the copious diuresis was collected in the indicated time intervals. In the first two hours (1,541 ml. urine volume) the 2.38 mg. of 5-HIAA excreted equaled the previous 24 hour 2.34 mg. of 5-HIAA. A single specimen containing the next 22 hours' excretion (4,780 ml.) of 8.08 mg. represented a 46 per cent recovery of administered 5-HTP in excess of the previous 24 hour control period. The diuresis apparently had no effect on the metabolism or excretion of 5-HIAA because these figures are similar to the data on all of the other patients in the study. The unusually low blood 5-HTP level probably reflects the thrombopenia secondary to nitrogen mustard therapy. There was no significant change in platelet serotonin levels.

Figure 3 indicates the average change in platelet 5-HT content during the three hours following 5-HTP injection. Although there is a terminal rise, this is just outside our range of error for 5-HT measurement. Such equivocal results may be explained by our low (0.1 to 0.3 mg. per Kg.) 5-HTP dosage as compared with animal experiments (11) where 400 to 1,000 times (60 to 150 mg. per Kg.) as much 5-HTP was given, produc-

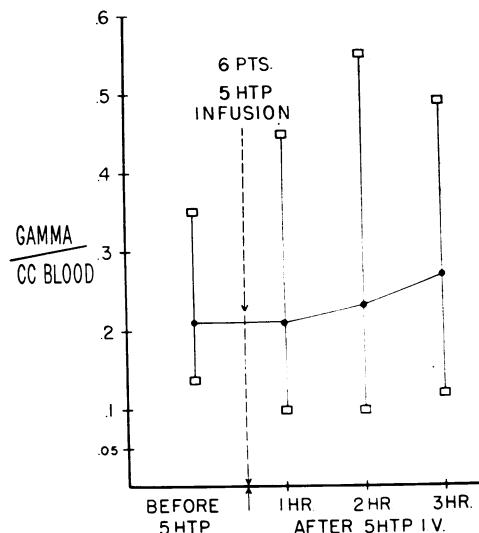


FIG. 3. RESPONSE OF BLOOD (PLATELET) 5-HYDROXYTRYPTAMINE TO 5-HYDROXYTRYPTOPHAN (5-HTP) INFUSION

Blocks represent ranges; dots, average.

ing a fourfold increase in blood 5-HT associated with markedly toxic central nervous system disturbances. These data confirm the statement made by Davidson, Sjoerdsma, Loomis and Udenfriend (12) that this dosage level of 5-HTP produced no effect on the blood serotonin in animals.

CLINICAL OBSERVATIONS

In the patients with hepatic insufficiency there was no change in tremors, mental confusion or reflex activity during the administration of 5-HTP, or for a three hour follow-up period. Patient

after cessation of I. V. 5-HTP. The only consistent observation was that of increased peristalsis, observed in four patients (V. O., P. H., A. F. and L. C.), with three of these complaining of abdominal discomfort (cramps and burning). Interestingly, J. K., who received four times the usual dose, displayed none of these effects. 5-HTP injection was not felt to contribute to the demise of the three patients dying three to seven hours following injection, since all three patients were extremely ill and were chosen for this reason as initial subjects.

DISCUSSION

Severe liver failure is frequently associated with serious disturbances of consciousness. This study was undertaken to determine whether the liver played any role in metabolism of serotonin and whether such metabolism might be deranged by liver failure. Figure 4 indicates the normal pathway of serotonin formation with its breakdown to 5-hydroxyindoleacetic acid. All of these steps have been demonstrated in animal tissues except the conversion of tryptophan into 5-hydroxytryptophan (13). As yet, the site of formation of this intermediate has not been demonstrated. It is quite clear from animal experiments that parentally injected 5-hydroxytryptamine is not able to enter the brain, whereas 5-hydroxytryptophan does enter the brain and causes a marked increase in the level of serotonin in that organ (11). It is most likely that the source of serotonin in the brain is 5-HTP formed elsewhere in the body. The conversion of tryptophan to 5-HTP is the type of reaction which is known to occur in the liver, the site of most hydroxylations. If the formation of 5-HTP were a function of the liver, one could expect that in severe liver failure there might be a defect in serotonin metabolism. The average 24 hour excretion of 5-HIAA for both groups (hepatic coma, 3.2 mg.; controls, 2.4 mg.) is in the low normal range when compared with 21 normal adults (average, 4.7 mg.; range, 2.3 to 9.7 mg. per 24 hours). The experiments herein reported do show that in severe liver disease 5-HTP can be converted to 5-HIAA, presumably by going through the 5-HT step.

The fact that only patients with liver disease show an effect of 5-HTP upon the electroen-

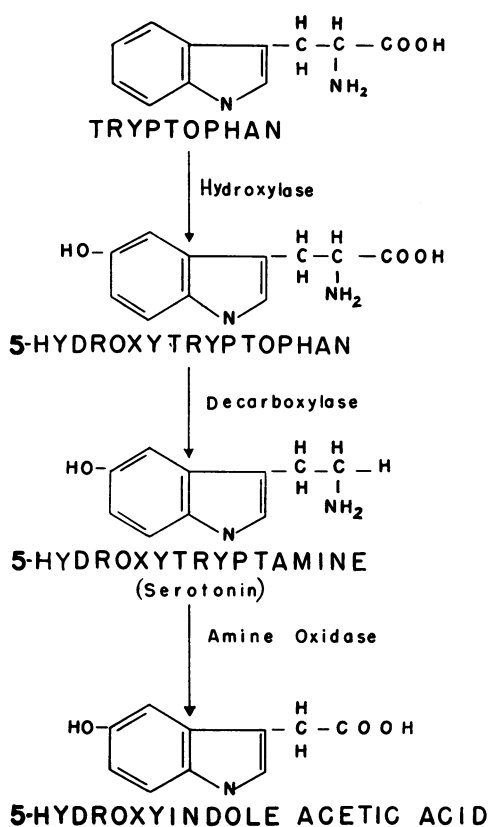


FIG. 4. METABOLIC PATHWAY OF 5-HYDROXYTRYPTAMINE (5-HT)

M. B., however, stated that she felt "quiet and restful" but demonstrated no improvement in her restlessness. Three patients (M. B., M. C. and P. H.) had significant increases in pulse rate which subsided following the 30 minute injection period. Two patients (A. F. and L. C.) demonstrated significant (average, 26/25) rises in blood pressure which subsided within 5 to 10 minutes

cephalogram suggests the possibility that within the brain a deficiency of serotonin exists, resulting from the inability of the patient with hepatic coma to convert tryptophan to 5-HTP. According to these results it appears as if there is some defect in serotonin formation in liver disease prior to 5-HTP (see Figure 4). Another possibility is that the observed electroencephalogram changes following infused 5-HTP simply represent a pharmacologic effect upon the brain akin to changes recorded in the gastrointestinal tract. Were this the case, however, it should have appeared in the controls.

SUMMARY

5-Hydroxytryptophan (5-HTP), 10 to 40 mg., was given intravenously to nine patients while electroencephalograms were recorded. In all five patients with hepatic coma, the slow activity diminished and the fast activity increased, altering the record in the direction of normal. In three patients with coma, not due to liver failure, and in one normal individual, there were no alterations in the electroencephalogram. Twenty-four hour urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA) accounted for 52 per cent of the 5-hydroxy-L-tryptophan administered. No definite defect was observed in the ability of patients with liver disease to metabolize 5-hydroxytryptophan as compared with a control group.

At the dosage levels utilized, infused 5-hydroxytryptophan produced no effect on blood serotonin.

In patients with hepatic insufficiency, there was no change in tremors, mental confusion or reflex activity. Abdominal discomfort and increased peristalsis were frequent.

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