ROLE OF 5-HYDROXYTRYPTAMINE IN TOXAEMIA AND ABORTION

By

S.C. Sen and S.K. Ganeriwal

Department of Physiology, Medical College, Nagpur

The clinical and pathological features of toxaemia have been produced by injec 5-Hydroxytryptamine (5-HT). Spies and Stone (15) found increase of blood pressure by jecting 5-HT in normotensive, hypotensive and hypertensive subjects. Studies of Ro and Benditt (12) show that 5-HT is responsible for edema formation in rats. Intraven infusion of 5-HT causes renal cortical necrosis in rats (9). The work of the latter auth also suggests a possible relationship between toxaemia of pregnancy and 5-HT. Krupp Krupp (7) found an apparantly increased plasma 5-HT level in toxaemia of pregnancy as co pared to that in non-pregnant and normal pregnant females. Urinary excretion of 5- does not change significantly in toxaemia of pregnancy unless complicated by chronic pertension (13). Urinary level of 5-Hydroxyindoleacetic Acid (5-HIAA), a chief metabo product of 5-HT has been estimated by Berry and Hughs (2) and Parikh and Bellare (10) cases of toxaemia of pregnancy. The former group of authors did not find any chang whereas the latter authors found a significantly reduced level of urinary 5-HIAA in toxae of pregnancy.

There are some experimental evidences which suggest the role of 5-HT in aborti It brings about contraction of mammalian uterus (1). It also elicits powerful rhythmi contractions of amniotc memberane of 10 to 12 days incubated chick (4). Erspamer (3) h utilised the mammalian uterus for bioassay of 5-HT. 5-HT can interrupt pregnancy at stages in mice (8). Schmidt and Pokorny (13) have reported a raised urinary excretion 5-HT in cases of inevitable abortions.

Though there is some evidence to show the role of 5-HT in toxaemia of pregnancy a abortion, very few attempts have been done to uncover its role in the above conditions and t results are equivocal. Therefore it was found of interest to estimate the level of 5-HT i serum during toxaemia of pregnancy and abortion, as well as it might also help introducti of some useful drugs in the treatment of above conditions.

MATERIALS AND METHODS

In the present work, level of serum 5-HT was determined in 11 cases toxaemia of pregnancy and 16 cases of inevitable abortion. All cases of toxaem belonged to third trimester of pregnancy (beyond 24 weeks of gestation) having group of common objective symptoms; hypertension (B.P. 130 mm/85 *mm* of

edema and proteinuria. Cases of inevitable abortion belonged to second trimester of pregnancy (from 12 to 24 weeks of gestation).

About 2 *ml.* of blood was obtained from each patient and was kept in sterile non-oxalated bottles and allowed to clot completely after which it was placed overnight in refrigerator and serum separated next morning.

Biological assay of serum 5-HT was done on isolated rat stomach strip preparation (16), using Tyrode's solution as the bathing fluid, the temperature of which was kept constant at 37°C. Oxygen was continuously passed in the bath. Atropine in 10^{-7} concentration was always added as a routine to the bathing fluid so that low concentrations of 5-HT could be assayed without being interfered with acetylcholine and histamine in small doses (16). Starting with the known concentrations of 5-HT , contractions with 0.1 *ml.* of serum were recorded. Doses of known 5-HT concentrations and 0.1 *ml.* of serum were alternately added till the response obtained by 0.1 *ml.* of serum directly matched with the response obtained by known concentrations of 5-HT solutions. The effect of 5-HT was identified as 5-HT by seeing the blocking effect of Cyproheptadine in doses of one microgram per ml. of the bath.

Level of 5-HT in non-pregnant females in childbearing age and normal pregnant females in second and third trimesters of pregnancy, estimated by us in our previous work (5) was used as a control for the present study. Comparison of serum 5-HT level in cases of inevitable abortion was done with that of non-pregnant and normal pregnant cases in second trimester of pregnancy. Comparison of serum 5-HT level in cases of toxaemia was done with that of non-pregnant and normal pregnant cases in third trimester of pregnancy.

RESULTS

The reults of estimation of serum 5-HT level in 11 cases of toxaemia of pregnancy are shown in detail in Table I. A representative graph of the biological estimation is given in Fig. 1.

Individual variations were present in this group. Average serum 5-HT level in these cases was found to be 29.28 ± 18.59 nanograms (*ngs.*) per *ml.* This when compared to the level of serum 5-HT in non-pregnant females (19.89 ± 10.63 *ngs.* per *ml.* (5) and the level in normal pregnant females during 3rd trimester of pregnancy (25.8 ± 12.83 *ngs.* per *ml.* (5) shows an apparent rise. This rise is insignificant at $P=0.05$.

The results of estimation of serum 5-HT level in 10 cases of inevitable abortion are shown in detail in Table II. A representative graph of the biological estimation is shown in Fig. 2.

Individual variations were very marked. Mean level of serum 5-HT in these cases was found to be 30.0 ± 14.31 *ngs.* per *ml.* When compared to the level of serum 5-HT in non-

TABLE 1

Level of serum 5-HT in females during pregnancy complicated with Toxaemia

No.	Blood pressure in *mm* Hg.	Level of serum 5-HT in *ngs./ml.*
1	140/100	45
2	130/92	13
3	130/90	35
4	140/100	42
5	145/100	2.5
6	140/104	12
7	230/130	37
8	130/90	6
9	148/90	45
10	180/110	33
11	130/90	58

TABLE II

Level of serum 5-HT in females during pregnancy complicated with inevitable abortion

No.	Blood pressure in *mm* Hg.	Level of serum 5-HT in *ngs./ml*
1	100/70	12
2	114/68	40
3	120/74	38
4	112/74	33
5	115/70	53
6	112/72	12
7	107/68	42
8	111/76	15
9	118/78	20
10	102/62	35

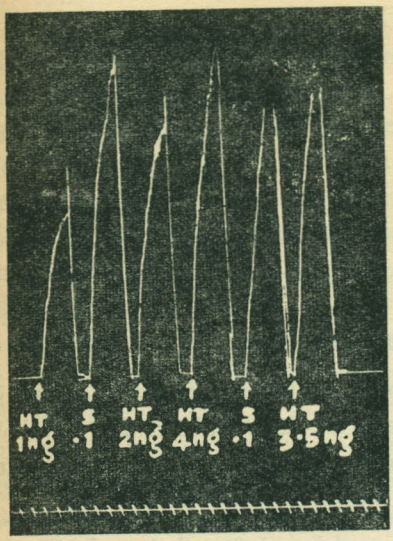

Fig. 1

Assay of the serum of the patient No. 3, *Table No. I, on caontractile response of rat stomach. HT Stands for* 5-*HT and 'S' stands for serum. Activity of* 0.1 *ml. of serum is equivalent to the activity of* 3.5 *ngs. of* 5-*HT (Time interval—*3 *seconds).*

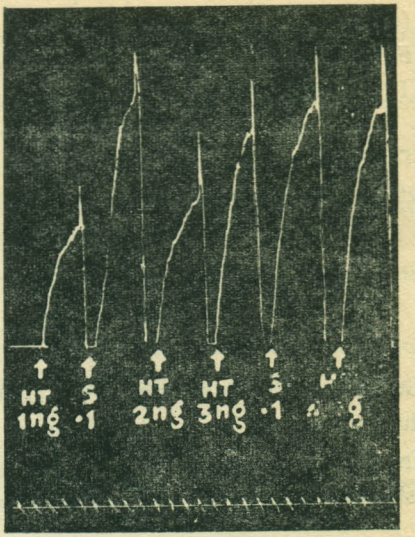

Fig. 2

Assay of the serum of the patient No. 2, *Table* II, *on contractile response of rat stomach. 'HT' stands for* 5-*HT and 'S' stands for serum. Activity of* 0.1 *ml. of serum is equivalent to the activity of* 4 *ngs of* 5-*HT (Time interval—*30 *seconds).*

pregnant females (19.89±10.63 *ngs.* per *ml.*) and that in normal pregnant females in second trimester of pregnancy (28.2±20.87 *ngs.* per *ml.*) shows an apparant increase. This increase is insignificant statistically at P=0.05.

DISCUSSION

From our results it is obvious that there is an apparant increase in 5-HT content in serum during toxaemia of pregnancy and abortion as compared to that in non-pregnant and normal pregnant females. When the results are scrutinised with the help of statistical methods, it was found that this increase of 5-HT in serum in the above conditions is statistically insignificant.

Our results of the serum 5-HT levels in toxaemia of pregnancy are in agreement with those of Berry and Hughs (2), and Schmidt and Pokorny (13). Increase in plasma 5-HT level as shown by Krupp and Krupp (7) might be apparant rather than significant. Decrease in 5-HIAA, excretion in urine with normal serum 5-HT level as shown by Parikh and Bellare (10) can be explained on the basis of decreased production or change in distribution of 5-HT. There is more possibility of a change in distribution as suggested by the work of Senior *et al.* (14), who found an increase in 5-HT level in placenta in cases of toxaemia of pregnancy without significant change in blood 5-HT level. Whether this change in distribution plays a role in causation of toxaemia is difficult to say but there is some indication of its role as suggested by

the beneficial effect of Methyldopa, an antagonist of 5-HT in cases of toxaemia of pr nancy (6).

Few data are available on estimation of serum 5-HT in inevitable abortion. Increa of 5-HT excretion in urine in inevitable abortion as shown by Schmidt and Pokorny (and no change in serum 5-HT level, as shown by us, can be explained on increased producti of 5-HT in this condition. This gives some indicaton for the role of 5-HT in inevitable abo tion which is supported by other evidences like interruption of pregnancy in mice by 5-H (8) and good therapeutic response of 5-HT antagonist in animals (11). A therapeutic tri with less toxic and more effective 5-HT antagonists is suggested in cases of inevitable abo tion.

SUMMARY AND CONCLUSIONS

Serum 5-hydroxytryptamine (5-HT) has been biologically estimated on the rat isolate stomach strip prepartion in toxaemia of pregnancy and inevitable abortion. Level of seru 5-HT in these conditions when compared to that in nonpregnant and normal pregnant fe males shows an apparant rise which is insignificant statistically at $P=0.05$.

Our results are discussed with those of others and it is inferred that 5-HT might b playing some role in toxaemia of pregnancy as well as in inevitable abortion.

A therapeutic trial with potent and less toxic 5-HT antagonists in inevitable abortio is suggested.

ACKNOWLEDGEMENTS

We extend our gratitudes to M/s Sandoz A.G., Basel for supplying us with a samp of 5-Hydroxytryptamine. We are thankful to Dr. B.B. Gaitonde, Professor of Pharmacolog Grant Medical College, Bombay for giving us Cyproheptadine for the present work.

REFERENCES

1. Abrahams, V.C. and M. Pickford. The effect of 5-Hydroxytryptamine on the uter of conscious and of anaesthetised dogs. *Brit. J. Pharmacol.* **11** : 50, 1956.
2. Berry, K.W. and M.L. Hughes. 5-Hydroxyindoleacetic Acid excretion in Pregnancy *Obstet. Gynec.* **14** :612, 1959.
3. Erspamer, V. Pharmacological studies on enteramine (5-Hydroxytryptamine); influenc of sympathomimetic and sympatholytic drugs on physiological and pharmacological ac tions of enteramine. *Arch. Internat. Pharmacodyn.* **93** : 293, 1953.
4. Evans, D.H.L. and H.O. Schild. Reactions of nerve free and chronically denervated plai muscle to drugs. *J. Physiol.* **122** : 63, 1953.
5. Ganeriwal, S.K. and S.C. Sen. Estimation of 5-Hydroxytryptamine in normal human pregnancy. *Ind. J. Physiol. and Pharmacol.* **10** : 37, 1966
6. Hans, S.F. and H. Kopelman. Methyldopa in treatment of severe toxaemia of pregnancy. *Brit. Med. J.* **1** : 736, 1964.

7. Krupp, P. and I. Krupp. Serotonin and toxaemia of pregnancy. *Obstet. Gynec.* **15** : 237, 1960.
8. Lindsay, D., E. Poulson and J.M. Robson. The effect of 5-Hydroxytryptamine on pregnancy. *J. Endocr.* **26** : 85, 1963.
9. Page, E.W. and M.B. Glendening. Production of renal cortical necrosis with serotonin (5-Hydroxytryptamine); theoretical relation to abruptio placentae. *Obst. and Gynec.* **5** : 781, 1955.
10. Parikh, M.N. and R.A. Bellare. Urinary excretion of 5-Hydroxyindoleacetic acid in normal and toxaemic pregnancy. *J. Obstet Gynaec. Brit. Comm.* **69** : 539, 1962.
11. Poulson, E. and J.M. Robson. Prevention by antagonists of the toxic actions of 5-Hydroxytryptamine on pregnancy. *Brit. J. Pharmacol.* **21** : 150, 1963.
12. Rowley, D.A. and E.P. Benditt. 5-Hydroxytryptamine and histamine as mediators of the vascular injury produced by agents which damage mast cells in rats. *J. Exper. Med.* **103** : 399, 1956.
13. Schmidt. W. and J. Pokorny. The significance of serotonin in obstetrics and gynaecology. pregnancy, labour and puerperium. *Zbl. Gynak.* **84** : 201, 1962 quoted by Bruce Eton, *J. Obstet. Gynaec. Brit. Comm.* **69** : 694, 1962. (Abst. No. 136).
14. Senior, J.B., I. Fahim, F.M. Sullivan and J.M. Robson. Possible role of 5 Hydroxytryptamine in toxaemia of pregnancy. *Lancet.* **2**: 553, 1963.
15. Spies, T.D. and R.E. Stone. Effect of serotonin on blood pressure and lack of effect of antimetabolite. *J.A.M.A.* **150** : 1599, 1952.
16. Vane, J.R. Sensitive method for the assay of 5-Hydroxytryptamine. *Brit. J. Pharmacol* **12** : 344, 1957.