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THE 5-HYDROXYTRYPTAMINE CONTENT OF THE PLACENTA, FOETUS AND SOME MATERNAL TISSUES DURING PREGNANCY IN THE RAT

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The results obtained from the measurement of the 5-hydroxytryptamine (5HT) content of mouse tissue during pregnancy (Robson & Senior, 1964) led us to undertake a similar investigation in the rat. Dixon (1959) measured the 5HT level in rat foetuses, and found that it reached a peak on the first day after birth, after rising steadily from about the fifteenth day of gestation.

Several workers (Nachmias, 1960; Karki, Kuntzman & Brodie, 1962) have investigated the level of 5HT in the brain of the newborn rat, and have found it to be about one-third of that found in the adult rat brain. Nachmias (1960) also showed that the amount of amine oxidase in the rat brain at birth was much lower than in the adult brain.

In the current experiments the levels of 5HT in the placenta and foetus have been measured in the second half of pregnancy, as have some of the levels in other maternal tissues. In an attempt to account for the amount of 5HT found in the untreated placenta, the maternal blood content of the placenta in the latter half of pregnancy was measured, and this was correlated with the maternal blood level of 5HT. Following the findings by Correll, Lyth, Long & Vanderpoel (1952) and Waugh & Pearl (1960) that 5HT produced deleterious effects on pregnancy in the rat, the level of 5HT was measured in the placenta and foetus after the administration of this drug. As 5HT treatment of the mother caused a rise in the 5HT level of the placenta it seemed of interest to investigate the effect of monoamine oxidase inhibitors, particularly as these substances had failed to change the level of 5HT in the mouse placenta (Robson & Senior, 1964).

METHODS

The experiments were performed on mature Wistar albino rats, weighing 250 to 400 g. They were housed in the Animal House, Guy's Hospital Medical School, and allowed food and water *ad libitum*. The food consisted of rat cake obtained from the North East Agricultural Society, Aberdeen. The pregnancy was dated by finding spermatazoa in the vaginal smear. The animal was then isolated from the male and pregnancy was confirmed from the 12th day onward by palpation.

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Extraction and assay of 5HT from the tissues

The animals were killed by a blow on the head and the tissues were removed immediately. For tissues at parturition, the animal was allowed to deliver two or three foetuses, then killed in the same manner and the tissues taken for extraction.

Two methods of obtaining blood for extraction were used, and both gave similar levels of 5HT. In some animals a subcutaneous injection of heparin (2,500 units/kg) was given 1 hr before death brought about by an overdose of chloroform. The heart was then exposed and blood was withdrawn from the left ventricle by means of a long siliconed pipette. In the other method the animal was killed by a blow on the head and the heart was exposed. Blood from the heart (usually 1 ml.) was withdrawn into a siliconed syringe.

The method of extraction and biological assay using the rat fundus strip preparation, and biochemical estimation, have been described previously (Robson & Senior, 1964). All the assay results are expressed as ng of 5HT base. Biochemical and means and standard deviations are given in the text. Estimations were carried out as confirmatory assays in all experiments except those involving amine oxidase inhibitors.

Histological examination for mast cells

Fresh tissue spreads were made from specimens of placentae, and fixed in absolute alcohol. They were stained with toluidine blue (0.8%, w/v, aqueous), washed with 50% (v/v) alcohol and then through xylene for mounting. Portions of other placentae were fixed and mounted in paraffin, then stained in a manner similar to that described by Riley & West (1953).

Ovariectomy

Rats 17 days pregnant were ovariectomized bilaterally by the dorsal route, and abortive parturition occurred on the 21st day of pregnancy. The uterine contents and blood were collected and assayed for 5HT. One group of pregnant rats was ovariectomized on day 17 and then treated with progesterone, 12 mg/kg in oil twice a day by the subcutaneous route, until killed on day 21. The uterine contents and blood were taken for assay.

Measurement of the maternal blood volume of the placenta

The method used to measure the maternal blood volume of the placenta in rats was similar to that employed in the experiment in mice (Robson & Senior, 1964). The erythrocytes were labelled using a sterile isotonic solution of sodium [^{51}Cr]-chromate and were washed and resuspended in plasma saline to give an activity of 50 μc/ml. of blood. Labelled erythrocytes with an activity of about 20 μc/ml. (0.4 ml.) were injected intravenously into rats at various stages of pregnancy. The animals were killed after 30 min and the placentae and foetuses were removed, together with a known volume of maternal blood and various other maternal tissues. The radioactivity was measured using a well-crystal scintillation counter. After the tissues had been weighed, the volume of maternal blood in each tissue could be calculated. Each result represents the mean of estimations made in two or more rats.

Injection of 5HT

Rats 14 days pregnant were injected subcutaneously with 5HT creatinine sulphate (May & Baker), 40 mg/kg, and then killed 1 hr later. The uterine contents and blood samples were removed and assayed for 5HT.

Injection of HP 1325, p-*di*(2-*hydrazinoethoxy*)*benzene hydrochloride*

This is an amine oxidase inhibitor. All the injections were subcutaneous. One group of rats received a single dose of 100 mg/kg on day 22 of gestation 5 hr before killing and removal of the tissues for assay. Other groups received treatment from days 17 to 21 in daily doses of 100, 80 and 50 mg/kg and the animals were killed on day 21 or 22. In all groups blood and tissues were removed for assay immediately after death, only living foetuses and associated placentae being taken for assay.

Injection of iproniazid

Rats 17 days pregnant were injected subcutaneously daily with iproniazid (80 mg/kg) until parturition. The animals were killed at parturition and living foetuses with associated placentae were taken for assay, together with maternal blood samples.

RESULTS

5HT level of the foetus and placenta during pregnancy

The level of 5HT was measured from the 12th day of gestation to parturition. Sufficient material for assay could not be collected before the 12th day. The results are shown in Figs. 1 and 2. The placental level of 5HT appeared to increase from the 12th to the 14th day and then showed no striking change until parturition when there was a marked fall. The difference between the placental levels for the 22nd day and parturition is highly

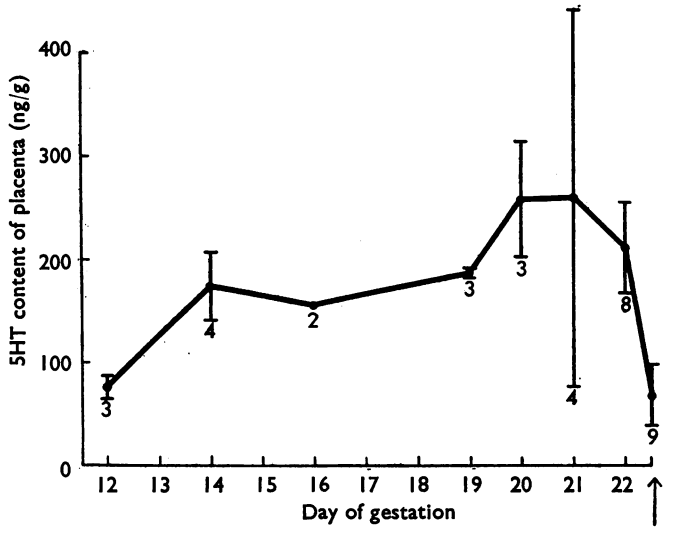

Fig. 1. Placental content of 5HT at various stages of pregnancy. Means and standard deviations are shown. Each result represents an assay on all the placentae obtained from one rat. The number of such assays is indicated for each stage of pregnancy. The arrow indicates the time of parturition.

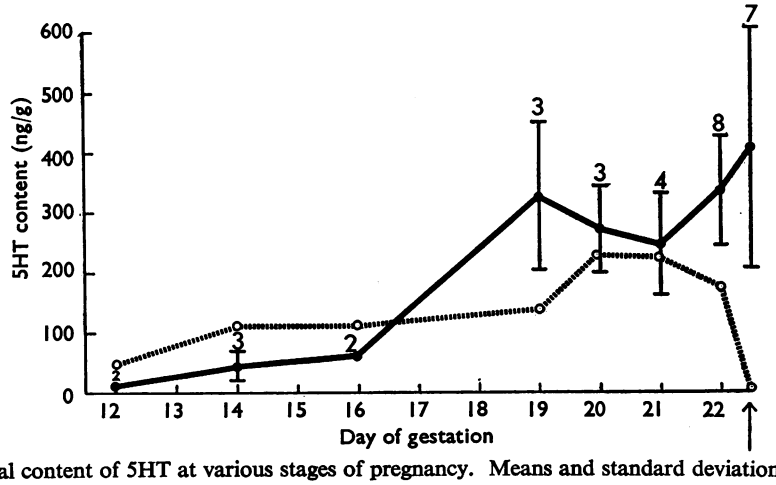

Fig. 2. Foetal content of 5HT at various stages of pregnancy. Means and standard deviations are shown. Each result represents an assay on all the foetuses obtained from one rat. The number of such assays is indicated for each stage of pregnancy. The broken line indicates the amount of 5HT in the placenta, excluding the maternal blood, at various stages of pregnancy, calculated on the assumption that 1 ml. of blood weighs 1 g. The arrow indicates the time of parturition.

significant ($P<0.001$). The foetal level of 5HT was low up to the 16th day (less than 100 ng/g), but had reached about 300 ng/g of tissue by the 19th day, after which it remained fairly constant.

Maternal blood levels of 5HT

The maternal blood levels of 5HT were measured on different days of gestation to determine whether the change in placental level merely reflected a change in maternal blood level. The 5HT content of the blood showed no correlation with the stage of pregnancy. The level in nine pregnant rats was 382 ± 71 ng/ml. (mean and standard deviation). This included two animals in parturition in which the blood levels were measured as well as the placentae and in which the following results were obtained: maternal blood level 400 ng/ml., placental level 78 ng/g; maternal blood level 375 ng/ml., placental level 88 ng/g. Thus it follows that the maternal blood level of 5HT is not responsible for the fall in the placental 5HT level at parturition. The 5HT content of blood from nonpregnant rats was also measured, and the mean result from five animals was 390 ± 134 ng/ml. There was no significant difference between the 5HT levels in the blood of pregnant and nonpregnant rats. The mean of all the results gave a blood level of 385 ± 93 ng/ml.

Uterine levels of 5HT in pregnant and nonpregnant rats

The 5HT content of the uterus was determined in nonpregnant rats, though the stages of the oestrous cycle were not recorded, and also at various stages of pregnancy. There was no definite trend in the 5HT content of the uterus as pregnancy progressed. The mean level in eight pregnant animals was 259 ± 117 ng/g, and that for six nonpregnant rats was 87 ± 27 ng/g. The uterine level of 5HT was higher in the pregnant rat than in the nonpregnant rat, and the difference was significant ($P<0.01$).

5HT content of the spleen

The 5HT content of the spleen was very variable, and could not be correlated with the presence of pregancy or the stage of pregnancy. The mean content of 5HT in the spleens of ten rats (pregnant and nonpregnant) was $4{,}424 \pm 1{,}748$ ng/g.

Measurement of the blood volume of the maternal placenta

The blood volume of the maternal placenta was measured to see if the 5HT in the maternal blood could account for the amount of 5HT found in the placenta. The results are shown in Fig. 3. It will be seen that the maternal blood makes up about 7% of the whole placenta on the 12th day of gestation, rising to around 20% on the 14th day and remaining essentially unchanged until parturition. The blood content of the uterus remains at about 5% throughout gestation from day 12 onwards, showing no correlation with the stage of pregnancy.

Using the values on the 5HT content of the maternal blood, and knowing the percentage of maternal blood in the placenta, the results on the 5HT content of the placenta at various stages of pregnancy have been recalculated to show the 5HT content of the placenta, excluding the maternal blood (Fig. 2). It is noteworthy that at parturition this part of the placenta contains practically no 5HT.

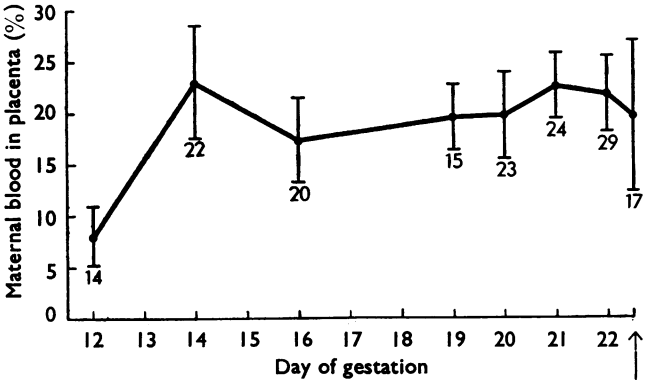

Fig. 3. Maternal blood volume of the placenta at various stages of pregnancy. Means and standard deviations are shown as well as the number of observations for each value. Each value represents an estimation on one placenta, the total number of placentae for each day of pregnancy being obtained from two or three rats. The arrow indicates the time of parturition.

Effect of injection of 5HT on placental and foetal levels

The effect of injecting 5HT into three 14-day pregnant animals was determined. The animals received 40 mg/kg of 5HT creatinine sulphate subcutaneously and were killed 1 hr later. In all three experiments all the foetuses were dead by that time. The 5HT content of the various organs and tissues are shown in Table 1. It can be seen that the content in the foetus had not risen above the normal level. The content of 5HT in the placenta, uterus and blood were markedly increased. The placental and blood levels had increased to about two to three times the normal level.

TABLE 1

THE EFFECT OF 5HT INJECTION (40 MG/KG, SUBCUTANEOUSLY) INTO THREE 14 DAY PREGNANT RATS ON THE 5-HYDROXYTRYPTAMINE LEVELS OF VARIOUS TISSUES

The values were obtained 1 hr after the injection and are means and standard deviations. The control values were those obtained for placenta and foetus on the 14th day of gestation. The control value for the blood is the mean of all results obtained. N.S. = not significant

	5HT level in		
Tissue	5HT-treated group (ng/g)	Control group (ng/g)	*P*
Foetus	55±23	42±25	N.S.
Placenta	414±115	173±32	<0.05
Uterus	426±93	259±117	<0.05
Blood	960±69	385±93	<0.001

Effect of ovariectomy on 5HT levels of uterine contents

Since the 5HT content of the placenta was found to be markedly decreased at parturition, experiments were performed to determine whether this would occur when abortion was produced by the removal of the ovaries. Two groups of four animals were taken. They were all ovariectomized bilaterally on day 17 of pregnancy, and one group received replacement therapy in the form of progesterone injection, each animal receiving 12 mg/kg of progesterone morning and evening. The other group was untreated after ovariectomy, and abortive parturition occurred on day 21, when all the foetuses were dead. All animals

were killed on day 21 and the 5HT level of the uterine contents was determined. In the animals treated with progesterone the foetuses were alive and appeared normal. The results of the 5HT assays for both groups of rats are shown in Table 2. It can be seen that the foetal levels of 5HT for both groups are similar, but the placental levels are very different. The placental level of the ovariectomized group not treated with progesterone was significantly lower than the level of the progesterone-treated group, which was similar to that in non-ovariectomized pregnant animals.

TABLE 2

THE EFFECT OF OVARIECTOMY, WITH OR WITHOUT SUBSEQUENT TREATMENT WITH PROGESTERONE, ON THE PLACENTAL AND FOETAL CONTENT OF 5HT

Two groups of four animals were ovariectomized on the 17th day of pregnancy. The first group went into abortive parturition on the 21st day and was then killed. The second group was treated with progesterone (12 mg/kg, morning and evening from the 19th to the 21st day). There were no signs of parturition on the 21st day when the animals were killed. Values are means and standard deviations

	5HT level in	
Treatment	Foetus (ng/g)	Placenta (ng/g)
Ovariectomy	305 ± 69	57 ± 34
Ovariectomy + progesterone	308 ± 54	275 ± 106

Histological examination for mast cells

As the placenta contained 5HT in excess of that found in the maternal blood, except at parturition, it was of interest to see if this 5HT was contained in mast cells. Examination of sections of 19-day placentae stained with toluidine blue failed to reveal the presence of any mast cells.

Effect of iproniazid on pregnancy

Ten pregnant rats received daily injections of iproniazid (80 mg/kg, subcutaneously) from day 17 of gestation until parturition. In nine of the rats parturition was delayed, while one went into labour on the 22nd day and gave birth to a normal live litter; this rat had a gross haemorrhage during parturition and died shortly after the foetuses had been delivered. Two rats became very weak during labour on the 23rd day of gestation and gross haemorrhage occurred; the foetuses were delivered alive, but died as the amniotic sacs were not removed. One rat delivered during the night of the 23rd day, but the foetuses, although born alive, died due to lack of attention from the mother. One rat delivered on the 24th day, and once again the foetuses were born alive but died due to lack of attention. In all cases labour was difficult and prolonged.

The remaining five rats were killed during parturition on the 23rd day and the uterine contents together with maternal blood samples were taken for 5HT assay. In three animals some of the foetuses were dead. The foetuses from one animal were weighed (mean weight 3.53 g) and the weights compared with those of normal foetuses at parturition (mean weight 6.79 g). The weights of the foetuses obtained from the animal treated with iproniazid were significantly lower than the weights of those taken from a normal animal ($P<0.001$). Table 3 shows the results of the 5HT assays. All the assays were carried out biologically. The 5HT content of the placentae (from live foetuses) was much higher than at normal

parturition ($P<0.001$). The 5HT content of the foetuses was not significantly different from that of animals at normal parturition. The maternal blood level of 5HT and that of the uterus was not significantly raised in the rats treated with iproniazid.

TABLE 3

EFFECT OF IPRONIAZID (80 MG/KG SUBCUTANEOUSLY) IN DAILY INJECTIONS FROM DAY 17 TO PARTURITION (23RD DAY OF PREGNANCY) ON THE TISSUE LEVELS OF 5HT

The control group shows the 5HT levels obtained for normal parturition (22nd day of pregnancy). The control level of 5HT in blood is a mean of all results obtained. The means are shown with standard deviations. There were five animals treated with iproniazid

	5HT level in		
Tissue	Iproniazid-treated group (ng/g)	Control group (ng/g)	*P*
Foetus	297±121	402±200	N.S.
Placenta	236±58	66±34	<0.001
Blood	436±50	385±93	N.S.
Uterus	208±12	259±41	N.S.

Effect of HP 1325 *on pregnancy*

Five pregnant rats were injected daily with HP 1325 (100 mg/kg, subcutaneously) from day 17 of pregnancy. Three rats were killed on the 21st day of pregnancy; all the foetuses were dead and resorbing. Two rats were killed on the 22nd day of pregnancy. One litter had completely resorbed, but the other litter contained one live foetus. This foetus, which was apparently normal, was taken for 5HT assay together with its associated placenta. The placenta contained 320 ng/g of 5HT, which is not outside the normal range. The foetal (340 ng/ml.) and maternal (400 ng/ml.) blood 5HT levels were also within the normal range. Further results could not be obtained to confirm this as all the other foetuses in the group were dead and resorbing. The mean maternal blood level of 5HT in the five animals treated with HP 1325, 100 mg/kg daily from day 17, was 444±52 ng/ml., which is not significantly different from the normal blood content of 5HT.

Two animals 22 days pregnant, received a single dose of HP 1325 (100 mg/kg, subcutaneously) 5 hr before killing. In both of these animals all the foetuses were alive and apparently normal. The mean maternal blood level of 5HT was 360 ng/ml. which is similar to the normal level of 5HT found in the rat blood. The mean placental level was 180 ng/g and the mean foetal level was 290 ng/g, that is results were similar to those found in normal animals on the 22nd day of pregnancy.

The daily dose of HP 1325 was then reduced in an attempt to find a dose which would not totally interrupt pregnancy. Two animals received doses of 80 mg/kg daily by the subcutaneous route from days 17 to 21 but when the animals were killed on day 22 all the foetuses in both litters were dead and in an advanced state of resorbtion. The mean maternal blood level of 5HT in the samples taken from these two animals was 464 ng/ml. which is in the range of the normal level.

Three pregnant rats received daily doses of 50 mg/kg of HP 1325 subcutaneously from day 17 to 21. They were killed on day 22 and all the foetuses in each litter were alive and apparently normal. The results of the 5HT assays of the uterine contents and maternal

blood are shown in Table 4. It can be seen that the mean blood level of 5HT for these rats was higher than that normally seen in rat blood ($P<0.001$). The placental and foetal levels of 5HT in the treated animals were similar to those obtained in normal animals on the 22nd day of pregnancy.

TABLE 4

EFFECT OF HP 1325 (50 MG/KG, SUBCUTANEOUSLY) IN DAILY DOSES FROM DAYS 17 TO 21 ON THE TISSUE LEVELS OF 5HT

The means are shown with standard deviations. There were three animals treated with HP 1325, while the controls for the placenta and foetus refer to the results obtained for the 22nd day of gestation. The blood level refers to all the results obtained

	5HT level in		
Tissue	HP 1325-treated group (ng/g)	Control group (ng/g)	*P*
Foetus	406±82	330±89	N.S.
Placenta	227±79	210±42	N.S.
Blood	540±31	385±93	<0.001

DICUSSION

These experiments have shown that the 5HT content of the placenta increases from the 12th to the 14th day of gestation, and thereafter shows no striking change until parturition when there is a marked fall. The 12th day is the earliest time at which such measurements could be made. The 5HT content of the maternal blood shows no changes which coincide with advancing gestation. The percentage of maternal blood in the placenta shows a similar pattern to that of the 5HT level in the placenta until parturition, that is rising from the 12th to the 14th day and then maintaining a steady level up to the 22nd day. However, at parturition the level of 5HT in the placenta falls, whereas the percentage of maternal blood present remains constant. This means that when the amount of 5HT in the placenta, excluding that present in maternal blood, is calculated, the 5HT level of the placenta at parturition is about zero. These results are particularly interesting when compared with those obtained for the mouse in similar experiments. The mouse placental level of 5HT rises steadily throughout pregnancy from day 12 and there is no fall at parturition, even when the 5HT present in the maternal placenta is excluded.

It is interesting to note that ovariectomy of the pregnant rat on day 17 causes abortive parturition on day 21, and the placental level of 5HT at this stage is very low and thus similar to that found in the normal parturient placenta. However, when pregnancy in the ovariectomized animals is maintained with progesterone, parturition does not occur on the 21st day and when the animals are killed on this day the placental level of 5HT is normal for this day of gestation. It would thus appear that the level of 5HT in the placenta is maintained as long as progesterone is present in the body and that when this is withdrawn, at parturition or following removal of the ovaries, there is a fall in the 5HT content of the placenta. Why there should be these differences in the placental content of 5HT in the rat and mouse is quite puzzling, particularly that the 5HT level rises at parturition in the mouse and falls rapidly in the rat (contrast Fig. 2 in Robson & Senior (1964) with Fig. 2 in the present paper). It may well be there is a difference in the metabolism (or storage) of the amine between the two species and this requires investigation. This possibility is supported

by the finding that amine oxidase inhibitors produce a rise in the placental 5HT in the rat but not in the mouse. An increase in the amine oxidase activity of the placenta in the rat at parturition would account for the fall in 5HT level, and this deserves investigation. Unfortunately Thompson & Tickner (1949), who investigated the amine oxidase content of the rat placenta, do not mention what happens at parturition.

The foetal level of 5HT in the rat is low up to the 16th day, but at the 19th day it has reached about 300 ng/g of tissue, and this level appears to remain fairly constant during the remainder of intrauterine life. Dixon (1959) also measured 5HT levels in the rat foetus; her results are lower than those reported here, but the assay methods were different and this may account for the discrepancies between the two values. Dixon used the rat colon method for the assay of 5HT and the presence of noradrenaline may interfere with the contractions of this tissue (Uuspaa & Uuspaa, 1962). The cause of the rise in the foetal content of 5HT is not known but, as reported for the mouse (Robson & Senior, 1964), it may coincide with the appearance of enterochromaffin cells in the foetus. It may be that the foetus is the primary site accounting for the rise in 5HT in the intrauterine tissues, and that an increase in monoamine oxidase causes the placental level to fall at parturition.

The changes in the 5HT content of the foetus and placenta following the administration of 5HT must now be considered. As in the mouse, the administration of 5HT to the mother causes death of the foetus within 60 min. Since there is no significant rise of 5HT in the foetus it appears that as in the mouse the toxic effect of 5HT is not due to a direct action on the foetus. The placental level of 5HT is significantly raised 1 hr after the injection of 5HT into the mother, and it therefore appears that death of the foetus is secondary to an effect of 5HT on the placenta. A calculation has been made based on the assumption that the amount of maternal blood in the placenta is about 23 % (for the 14th day of gestation) of the total placental weight, and that this maternal blood contains the same concentration of 5HT as is present in the systemic maternal blood; it is furthermore assumed that the 5HT content of the remainder of the placenta has not altered as a result of the 5HT administration. On this basis the theoretical value for 5HT in the placenta 1 hr after the injection of 5HT to the mother is 330 ng/g tissue, whereas the actual value from the 5HT assay was 414 ± 115 ng/g of tissue. These results are interesting, as it does appear that under these circumstances most of the rise in the 5HT content of the placenta is due to the rise in the 5HT content of the maternal blood present in the placenta. Similar findings have been reported in the mouse (Robson & Senior, 1964).

The effect of iproniazid on late pregnancy in the rat is rather unexpected. The level of 5HT in the placenta is significantly higher at parturition after treatment of the mother with iproniazid, and parturition is delayed and prolonged. Whether the high placental level of 5HT is the cause of the delay in parturition is not known. It is possible that in the rat normal parturition will not occur unless the 5HT content of the placenta falls. If this fall is prevented by the administration of iproniazid then the placental 5HT level does not decrease and parturition is delayed and the ensuing labour is difficult. On the other hand it is possible that some essential function of parturition is blocked by a direct action of iproniazid. The failure of treatment with iproniazid to raise significantly the maternal blood level of 5HT is unexpected. This rise in the placental level of 5HT following treatment with iproniazid in the rat differs from the results of similar treatment in the mouse; the mouse placental level was unaffected. However, it must be noted that treatment with

iproniazid in the mouse was from days 11 to 13 of gestation and in the rat treatment was from day 17 to parturition. It is interesting to note that treatment with iproniazid in both the rat and the mouse did not affect the maternal blood level of 5HT. HP 1325, a more potent monoamine oxidase inhibitor, in high doses brought about complete resorption of the foetuses in the second half of pregnancy. This is different from the results in the mouse, where in the second half of pregnancy HP 1325 was not toxic to the foetuses (Robson & Senior, 1964). However, in the rat, a lower dose of HP 1325 did not cause resorption of the foetuses but did raise the maternal blood level of 5HT. It may be that when the blood level is raised by a certain amount then the placental level of 5HT is affected and death of the foetus occurs. The action of HP 1325 in causing death of the foetuses may, however, be through a completely different mechanism and not through 5HT metabolism. The mechanism of action of these monoamine oxidase inhibitors on pregnancy requires further investigation.

SUMMARY

1. The 5HT content of the uterus, blood and spleen were determined in nonpregnant rats and at various stages of pregnancy including parturition. The 5HT level of the foetus and placenta was also determined in the second half of pregnancy.

2. The foetal level of 5HT was low up to the 16th day, increased up to the 19th day and then appeared to level out up to and including parturition. The placental level appeared to increase gradually up to the 14th day and then remained constant until parturition when it fell to a much lower level.

3. The placenta contained no mast cells; hence the 5HT could not be derived from this source.

4. Ovariectomy on day 17 caused abortive parturition on day 21, and when this occurred the 5HT level of the placenta had fallen to the normal parturient level. This finding could be reversed if the ovariectomized animal was maintained on progesterone.

5. 5HT was adminstered to pregnant rats and maternal tissue levels were determined 1 hr later, shortly after death of the foetus. The level of 5HT was raised significantly in the maternal blood, uterus and placenta, but not in the foetus.

6. The levels of 5HT in the uterine contents and maternal blood were measured after treatment of the mother with monoamine oxidase inhibitors. Iproniazid caused a delay in parturition and raised the placental 5HT level at parturition. HP 1325, *p*-Di(2-hydrazinoethoxy)benzene hydrochloride, in high doses caused resorption of the foetuses, and in lower doses raised only the maternal blood level of 5HT.

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