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COMPARATIVE EFFECTS OF HYPOPHYSECTOMY AND ADRENALECTOMY UPON PLASMA AND ADRENAL MONOAMINES IN PREGNANT AND NON-PREGNANT RATS

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1 The influence of hypophysectomy and adrenalectomy upon release and storage of adrenaline and noradrenaline during rat oestrous cycle and pregnancy has been studied.

2 Hypophysectomy during the pro-oestrous phase of the oestrous cycle increased plasma noradrenaline concentration which was unchanged, however, by similar treatment in pregnant females. After adrenalectomy during dioestrous and pro-oestrous phases, as well as on day 15 post-coitum, plasma noradrenaline showed an increase, although the increase in pregnant females was greater.

3 Adrenocorticotrophic hormone (ACTH) administration to non-pregnant and pregnant females increased plasma adrenaline values significantly, compared with control values. Treatment of adrenalectomized rats with hydrocortisone lowered plasma noradrenaline to control values in both non-pregnant and pregnant females.

4 Hypophysectomy produced a decrease in plasma adrenaline content, whilst ACTH treatment increased it. Plasma adrenaline disappeared completely after adrenalectomy, during the pro-oestrous phase and pregnancy, but extirpation of adrenals during the dioestrous phase still left appreciable amounts of adrenaline in plasma. Hydrocortisone treatment of both non-pregnant and pregnant adrenalectomized females resulted in the reappearance of plasma adrenaline

5 Adrenal stores of adrenaline and noradrenaline declined after hypophysectomy but the decreases were greater in pregnant females.

6 Compensatory administration of ACTH to hypophysectomized females increased adrenaline and noradrenaline content of adrenals to control non-pregnant female values during the pro-oestrous phase of the oestrous cycle but similar treatment in pregnant females resulted in an increase in adrenaline.

7 Although ACTH administration increased adrenal noradrenaline levels in pregnant hypophysectomized females, the mean value remained below that of non-operated pregnant females.

8 The results suggest that, during oestrous cycle and pregnancy the effects of pituitary and adrenal hormonal deficiency upon storage and release of monoamines differ quantitatively.

Introduction

Earlier studies suggest that the hormones of the adrenal cortex and the medullary monoamines act as a physiological unit (Britton, 1930; Ramey & Goldstein, 1957). Some of the physiological effects of adrenaline and noradrenaline do not occur in the absence of glucocorticoid hormones (Axelrod, 1963; 1965; Schayer, 1964). The isolation and characterization of the adrenal medullary enzyme, phenylethanolamine *N*-methyltransferase, provided a tool to study the possible link between adrenomedullary and adreno-cortical function (Axelrod, 1962). It has been reported that adrenaline content and activity of this enzyme in adrenal gland are greatly decreased after hypophysectomy in adult animals (Wurtman & Axelrod, 1965; 1966). Further investigations suggest that glucocorticoids in adrenal portal blood are essential for the conversion of noradrenaline to adrenaline, and for the activity of phenylethanolamine *N*-methyltransferase in the adrenal medulla (Wurtman, 1966; Parvez, Parvez & Youdim, 1975). Our recent studies also provide evidence to show that the rate of monoamine metabolism is reduced by a decrease in glucocorticoid concentration in the circulation (Parvez & Parvez, 1973a, b). Both monoamine oxidase and catechol *O*-

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methyltransferase activities are significantly higher in animals in which glucocorticoid production is blocked pharmacologically or surgically (Parvez & Parvez, 1972a, 1973c; Youdim & Holzbauer, 1976).

The present experiments were performed to compare the effects of hypophysectomy and adrenalectomy upon storage and release of adrenaline and noradrenaline between rats in the pro-oestrous phase of the oestrous cycle and pregnant rats. Plasma levels of adrenaline and noradrenaline were determined six days after hypophysectomy or adrenalectomy, during pro-oestrus or on day 15 post-coitum. The operated females also received compensatory administration of hydrocortisone or adrenocorticotrophic hormone (ACTH) to assess the effect of these two hormones during oestrous cycle and pregnancy.

Methods

Albino female rats of Sherman strain, obtained from Janvier, Paris, and weighing 250 ± 50 g, were housed at a constant temperature of 21°C with natural day and night cycles. They were fed with commercial laboratory food *ad libitum*. The rats were impregnated by keeping one male with seven females in a cage from 18 h 00 min to 09 h 00 min once only. Fertilization was defined as having occurred at 02 h 00 min. Thus, it was possible to estimate an approximate time of pregnancy (±7 hours). The animals were palpated abdominally 14 days later to verify the pregnancy. If positive, at 02 h 00 min they were considered to be 14.5 days pregnant. Under normal conditions parturition took place between 21.5 and 22 days of pregnancy (Parvez *et al.*, 1975).

Hypophysectomy and ACTH administration

Control female rats in pro-oestrus (non-pregnant) were identified by examining vaginal smears. Only those with well-defined symptoms of pro-oestrus were used. Pregnant females were used on the 15th day of gestation. Hypophysectomy was performed parapharyngealy under ether anaesthesia (Smith, 1926). Hypophysectomized animals were maintained on sucrose water together with normal laboratory food. All operated females were checked for effectiveness of operation after they were killed. Another group of non-pregnant and pregnant hypophysectomized females received daily injection of ACTH (1.3 iu/100 g body weight) from day 16 post-coitum to day 21 post-coitum. Hypophysectomy did not alter the time of parturition.

Adrenalectomy and hydrocortisone treatment

The animals were adrenalectomized bilaterally, either on day 15 of pregnancy or during the well-defined pro-oestrous phase of the oestrous cycle. They were given salt water in addition to commercial laboratory food. Some animals in each group received daily injections of hydrocortisone (3 mg/100 g body weight) for 6 days.

Isolation of adrenals and plasma

Five hours after the last injection the animals were killed by neck fracture and blood collected and adrenals excised within 1 minute. This procedure avoided shock. A maximum of 3 ml blood was taken from the abdominal aorta of each rat. Most samples of blood were free from haemolysis and only such plasma was used for catecholamine analysis.

Assay of adrenaline and noradrenaline in adrenals

The adrenals were carefully cleaned of fat, weighed and homogenized in 2 ml of 4% (w/v) trichloroacetic acid at 0°C. Adrenal adrenaline and noradrenaline were isolated according to the technique of Euler & Lishajko (1961) using the trihydroxindole reaction for fluorimetric estimation.

Assay of plasma catecholamines

Heparinized blood from 5 rats was pooled in a glass centrifuge tube containing 2 ml of potassium fluoride, 2% (w/v) and potassium thiosulphate, 3% (w/v). The blood was centrifuged at 4°C for 10 min at 4000 *g* and adrenaline and noradrenaline in plasma were isolated by adsorption on acid activated aluminium oxide (Euler & Lishajko, 1959). The batch process was preferred to column as recoveries were better (Anton & Sayre, 1962). One gram of alumina was washed twice with glass distilled water and the plasma added to a centrifuge tube. The pH was adjusted to 8.4 by glass electrode pH meter with continuous shaking for 4 minutes. The tubes were then centrifuged at 2000 *g* for 1.5 min and the supernatant discarded. The alumina was washed with 20 ml of distilled water and both adrenaline and noradrenaline were eluted with 4 ml of 0.25 N acetic acid. The trihydroxindole procedure was employed for simultaneous estimation of both amines.

All the results were subjected to statistical analysis by Fisher's *t* test. Mean values are expressed ± s.e. mean.

Results

Plasma adrenaline after hypophysectomy and adrenalectomy

Figure 1 shows the influence of pituitary ablation upon plasma adrenaline concentration in non-pregnant and pregnant females. After hypophysectomy, values in non-pregnant female rats decreased significantly, by

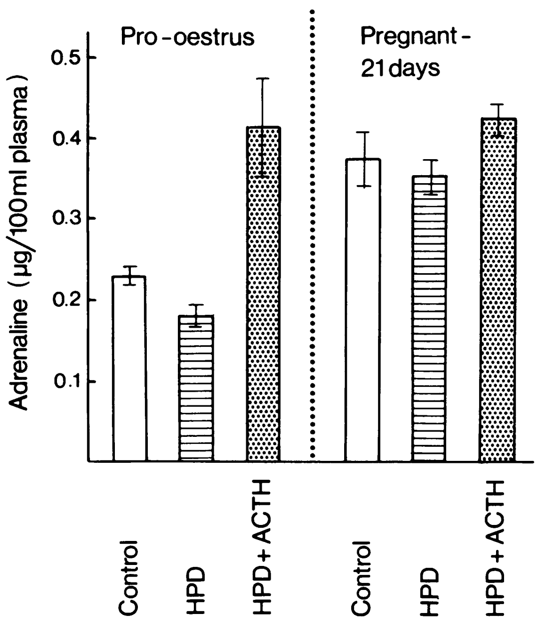

Figure 1 Influence of hypophysectomy in female rats during pro-oestrous phase of the oestrous cycle or on 15th day post-coitum upon plasma adrenaline content. The animals were killed 6 days later. Hypophysectomized rats (HPD); Hypophysectomized rats receiving daily injections of ACTH (HPD + ACTH). Each group represents the mean value of at least 8 to 12 individual values. Vertical lines show s.e. mean. Statistical differences between the different groups are as follows:

Pro-oestrus		
Control	vs HPD	$P<0.05$
Control	vs HPD+ACTH	$P<0.01$
HPD	vs HPD+ACTH	$P<0.001$
Pregnant 21 days		
Control	vs HPD	NS
Control	vs HPD+ACTH	NS
HPD	vs HPD+ACTH	NS

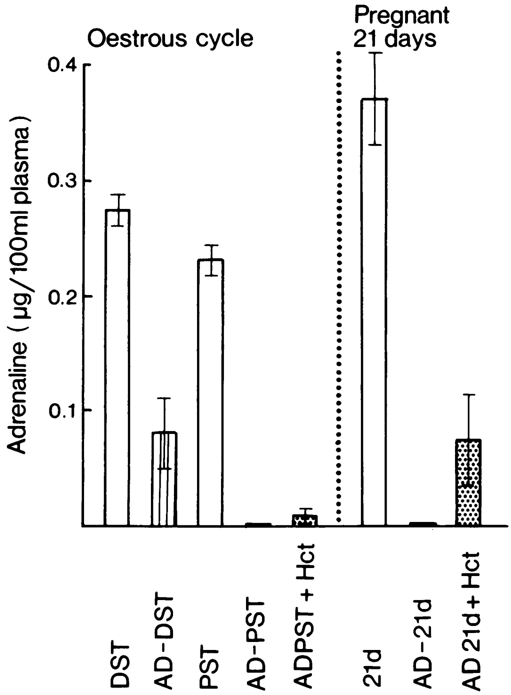

Figure 2 Plasma adrenaline levels in female rats adrenalectomized during dioestrous or pro-oestrous phase of the oestrous cycle or on 15th day of pregnancy. The animals were killed 6 days after operation, some receiving hydrocortisone supplementation. The mean value for each group was calculated from at least 12 to 20 individual values. Dioestrus (DST); pro-oestrus (PST); adrenalectomized rat (AD); hydrocortisone (Hct); and adrenalectomized 21 day pregnant rats (AD21d). Statistical differences between groups are as follows:

Oestrous cycle		
DST	vs AD−DST	$P<0.001$
PST	vs AD−PST+Hct	$P<0.001$
Pregnant–21 days		
AD–21d	vs AD−21d+Hct	$P<0.001$

20% compared with controls. The pregnant females showed a small but not significant decrease in plasma adrenaline concentration after pituitary ablation. Compensatory treatment with ACTH (1.3 iu/100 g body weight daily) for 6 days brought about a pronounced increase in hypophysectomized non-pregnant females but similar treament in hypophysectomized pregnant females produced no significant effect.

The effect of adrenalectomy on plasma adrenaline concentration in pregnant and non-pregnant rats is shown in Figure 2. Females adrenalectomized during pro-oestrus or on day 15 post-coitum manifested a complete absence of adrenaline in their plasma. Females adrenalectomized during dioestrus showed a relative rather than absolute decrease in plasma adrenaline. Treatment of adrenalectomized pro-oestrous females with hydrocortisone (3 mg/100 g body weight) for 6 days increased plasma adrenaline concentration. Similar hydrocortisone dosage in females adrenalectomized on day 15 of pregnancy produced a significant increase in plasma adrenaline level although the mean value remained well below that of controls.

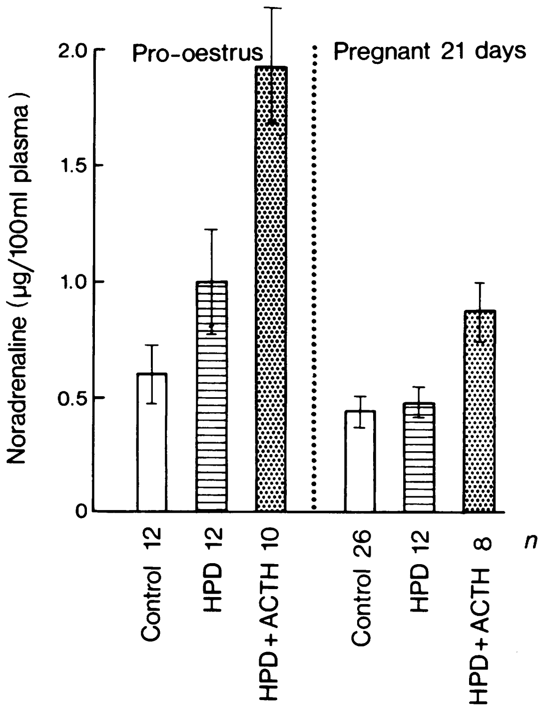

Figure 3 Plasma noradrenaline levels in non-pregnant and pregnant female rats subject to hypophysectomy. Each group represents the mean value of at least 8 to 26 rats. Hypophysectomized female rats receiving ACTH treatment daily (HPD).
Statistical differences between groups are as follows:

Pro-oestrus		
Control	vs HPD	NS
HPD	vs HPD+ACTH	$P<0.01$
Pregnant 21d		
HPD	vs HPD+ACTH	$P<0.01$

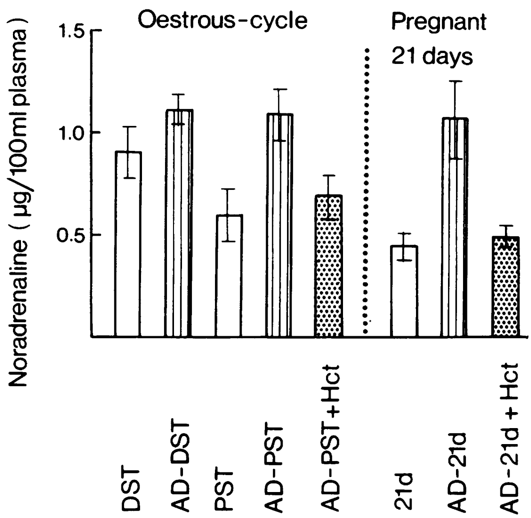

Figure 4 Effect of adrenalectomy on plasma noradrenaline levels of non-pregnant female rats during di-oestrous (AD–DST) or pro-oestrous phase (AD–PST). The pregnant animals were adrenalectomized on day 15 post-coitum (AD–21d). similar groups also received daily injections of hydrocortisone (Hct). All animals were killed 6 days after operation, some receiving hydrocortisone supplementation. Each group represents the mean value of at least 10 to 26 rats. Vertical lines show s.e. mean.
Statistical differences between groups are as follows:

Oestrous cycle		
PST	vs AD–PST	$P<0.02$
AD–PST	vs AD–PST+Hct	$P<0.02$
Pregnant 21d		
21d	vs AD–21d	$P<0.01$
AD–21d	vs AD–21d+Hct	$P<0.01$

Plasma noradrenaline after hypophysectomy and adrenalectomy

Figure 3 shows the effects of hypophysectomy on plasma noradrenaline concentration in pregnant and non-pregnant rats, 6 days after operation. Pituitary ablation during pro-oestrus resulted in a 40% increase in plasma value; similar treatment in pregnant rats, however, produced little change. Daily administration of ACTH to pro-oestrous hypophysectomized females resulted in a 93% increase of noradrenaline when compared with control operated females. Pregnant females treated with ACTH responded in a similar manner to non-pregnant females although the increase was somewhat less marked (80%).

Adrenalectomy in pregnant and non-pregnant females resulted in a highly significant increase in plasma noradrenaline concentration in the former (143% higher than the non-operated pregnant value, Figure 4). Adrenalectomy on oestrous rats had a similar qualitative effect but differed quantitatively from that in pregnant females. Adrenalectomy during dioestrus and pro-oestrus increased plasma noradrenaline concentration by 24 and 85% respectively, the latter being significantly different from its pro-oestrous control value. Replacement therapy of non-pregnant and pregnant adrenalectomized rats with hydrocortisone decreased plasma noradrenaline values, the means then being similar to those of non-operated controls (Figure 4).

Adrenal catecholamine content in non-pregnant and pregnant hypophysectomized rats

Figure 5 compares adrenaline content of the adrenal glands of non-pregnant and pregnant females after

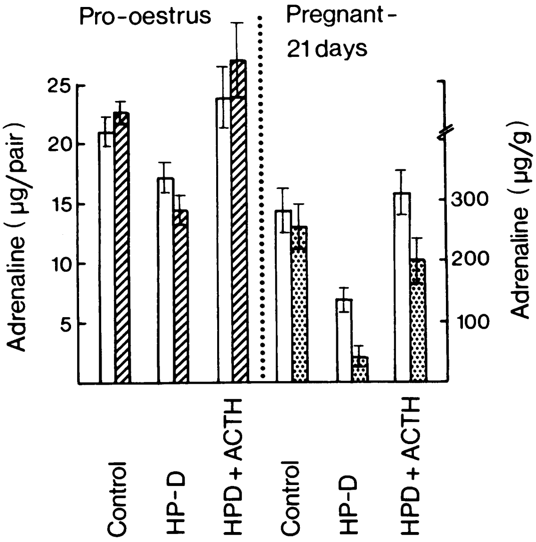

Figure 5 Influence of hypophysectomy (HPD) on adrenal adrenaline content in female rats during pro-oestrous phase of the oestrous cycle or on 15th day of pregnancy. The animals were killed 6 days after operation. The hatched columns show values as µg/g of adrenal gland, the open columns as µg/pair of adrenals. Each group represents the mean of at least 10 to 26 rats. Vertical lines show s.e. mean.
Statistical differences are as follows:

		µg/pair	µg/g
Pro-oestrus			
Control	vs HPD	$P<0.01$	$P<0.005$
HPD	vs HPD+ACTH	$P<0.02$	$P<0.005$
Pregnant 21d			
Control	vs HPD	$P<0.005$	$P<0.001$
HPD	vs HPD+ACTH	$P<0.01$	$P<0.01$

After ACTH administration, mean values in non-pregnant and pregnant hypophysectomized females were not significantly different from control values.

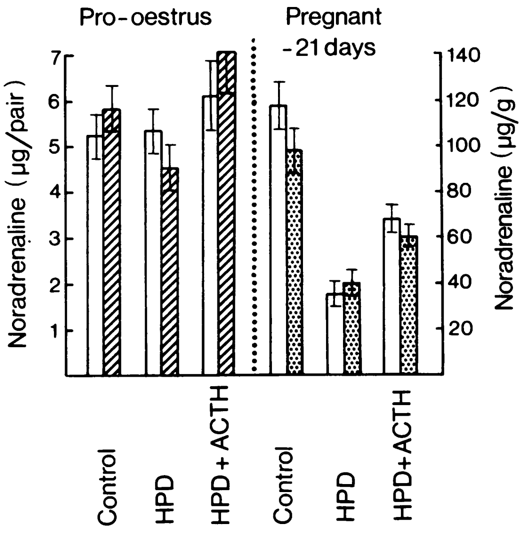

Figure 6 Influence of hypophysectomy (HPD) on adrenal noradrenaline content in female rats during pro-oestrous phase of the oestrous cycle or on the 15th day of pregnancy. All the animals were killed 6 days after operation. One group of each type also received ACTH throughout the post-operative period. Mean values are calculated from 10 to 26 individual rats. Vertical lines show s.e. mean.
The statistical differences between the groups are as follows:

		µg/pair	µg/g
Pro-oestrus			
Control	vs HPD	NS	NS
HPD	vs HPD+ACTH	NS	$P<0.05$
Pregnant 21d			
Control	vs HPD	$P<0.01$	$P<0.01$
HPD	vs HPD+ACTH	$P<0.01$	$P<0.05$
Control	vs HPD+ACTH	$P<0.01$	$P<0.01$

hypophysectomy. The results are expressed both as µg/pair of glands and µg/g adrenal weight. After hypophysectomy, total adrenal adrenaline of pro-oestrous rats decreased by 19% and the decrease was more marked (38%) when expressed as µg/g. Pituitary ablation in pregnant females produced a significant decrease in adrenal adrenaline content (53% when expressed as µg/pair and 84% as µg/g adrenal). Daily administration of ACTH to pro-oestrous hypophysectomized females resulted in an increase in adrenal adrenaline content, more pronounced when the results were expressed as µg/g adrenal (87% higher than pro-oestrous hypophysectomy value). The daily treatment of hypophysectomized pregnant rats with ACTH also produced a significant increase in adrenal adrenaline content but in this case, ACTH-induced increases were greater when expressed as µg/pair of glands, a result contrasting with that obtained in non-pregnant females.

The effects of hypophysectomy upon adrenal noradrenaline content in pregnant and pro-oestrous females are illustrated in Figure 6. The operation brought about a slight decrease in non-pregnant rats but similar treatment in pregnancy resulted in a significant decrease in adrenal noradrenaline content, 70% lower when expressed as µg/pair and 59% lower expressed as µg/g adrenal. Daily injections of ACTH for 6 days resulted in increased noradrenaline values in adrenals from both non-pregnant and pregnant females. After ACTH treatment, mean non-pregnant noradrenaline values in hypophysectomized females were not significantly different from those in non-operated rats. Daily ACTH injection to pregnant hypophysectomized females increased adrenal noradrenaline content by 94% (μg/pair of adrenals) or 50% (μg/g adrenal). However, when compared with hypophysectomized non-pregnant rats, noradrenaline content was not restored to control levels.

Discussion

The results of the present investigation concerning the influence of hypophysectomy upon plasma adrenaline concentration in non-pregnant females are compatible with the suggested role of adrenocortical hormones in the processes of monoamine release and biosynthesis (Axelrod, 1965; 1968). After hypophysectomy of pro-oestrous females, a significant decline in adrenal adrenaline stores results which presumably mirrors the decreased plasma adrenaline content since most circulating adrenaline derives from adrenomedullary secretion (Euler, Franksson & Hellstrom, 1954). Under normal conditions, ACTH release stimulates glucocorticoid production which is essential for the maintenance of adrenaline stores in the adrenal medulla; they cause induction of the medullary enzyme, phenylethanolamine-*N*-methyltransferase (PNMT), responsible for noradrenaline *N*-methylation to adrenaline (Wurtman & Axelrod, 1965, 1966). After hypophysectomy, absence of ACTH secretion prevents adrenal glucocorticoidogenesis which in turn directly affects adrenal adrenaline stores and PNMT activity (Axelrod, 1965; Wurtman, 1966). Hypophysectomy in pregnant females had similar quantitative effects on adrenaline storage and release as in non-pregnant female rats but the reduction in adrenal adrenaline was greater. This finding can be interpreted by taking into consideration the physiological alterations in concentration of corticosteroids and other related hormones during the course of pregnancy. The concentrations of many steroid hormones fluctuate widely during pregnancy, conceivably modifying monoamine storage, release and metabolism in pregnant animals. More specific evidence implicating endocrine gland secretions in monoamine regulation can be seen when hypophysectomized females receive daily injections of ACTH. This treatment increases plasma and adrenal adrenaline concentration to normal levels in pregnant hypophysectomized females; in non-pregnant hypophysectomized females receiving similar treatment the increase was much higher than that observed for pregnant females.

The complete disappearance of plasma adrenaline after adrenalectomy during pro-oestrus and on day 21 post-coitum supports the original assertion of Euler *et al.* (1954) that the adrenal medulla is the main source of adrenaline in the body. Even so, the presence of adrenaline in the plasma of non-pregnant females after adrenalectomy during dioestrus provides evidence in favour of the observations reported by Axelrod (1968) regarding the presence and release of adrenaline in heart and other organs. Some evidence for the presence of extra-adrenal sources of adrenaline is provided by studies on pregnant and non-pregnant adrenalectomized rats receiving hydrocortisone. Such treatment results in the appearance of adrenaline in the plasma. Further support for this hypothesis comes from the fact that there was no evidence of adrenal regeneration in the animals investigated.

The increased plasma noradrenaline content after adrenalectomy in dioestrus and pro-oestrus, as well as on day 21 of pregnancy, points to an activation of adrenergic nerve activity. It has been shown that adrenalectomy increases the activity of central noradrenaline-containing neurones after a certain latency (Javoy, Glowinski & Kordon, 1968). Other observations on the effects of this operation on noradrenaline metabolism and on the role of adrenal hormones in maintaining tissue stores of noradrenaline during increased sympathetic activity (Avakian & Vogt, 1966) are consistent with our findings. Further evidence, relating to stimulation of noradrenergic function due to lack of adrenocortical hormones, is seen in Figure 4 where we record a return of plasma noradrenaline levels to control values after daily administration of hydrocortisone to non-pregnant and pregnant adrenalectomized rats.

Hypophysectomy does not modify adrenal noradrenaline concentration in male rats and this finding is also valid for females hypophysectomized at pro-oestrus. The slight rise observed in plasma noradrenaline concentration in non-pregnant hypophysectomized females may be related to changes in uptake and metabolism (Iversen, 1973). The marked decline in adrenal noradrenaline content in pregnant females after hypophysectomy suggests that noradrenergic activity during pregnancy is more sensitive to changes in pituitary hormone concentrations than that in the non-pregnant state. ACTH treatment restored adrenal noradrenaline values to normal in non-pregnant animals but the mean value in pregnancy remained far below that of controls, thus suggesting the possible involvement of other hormones. The marked increase in plasma noradrenaline concentration after ACTH treatment in both non-pregnant and pregnant hypophysectomized females confirms earlier observations that ACTH has a direct potentiating effect on adrenaline accumulation and secretion (Parvez, Parvez & Roffi, 1974). Our other studies on the role of hypophyseo-adrenocortical function in the processes of monoamine metabolism provide further support for this view (Parvez & Parvez, 1972b; 1974; Holzbauer, Mitchell & Youdim, 1975).

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