Developmental patterns of levels of corticosterone and of corticosterone binding in the serum of female rats: effects of ovariectomy and adrenalectomy

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Abstract. Corticosterone concentrations and corticosterone binding in the serum were studied in immature female rats, using radioimmunoassay and batchwise gel equilibration techniques. A parallel developmental pattern was found for corticosterone levels and its serum binding with a neonatal drop, followed by low levels until 12 days of age and a rise between 12 and 28 days of age. Effects of adrenalectomy, of ovariectomy, of the combined operation and of sham-operations, performed at various ages, were also studied. Adrenalectomy performed at 5 days of age did not decrease serum corticosterone concentrations within a 6-day period whereas it did in older rats. Complete disappearance of corticosterone from the blood occurred only in adult rats after combined adrenalectomy/ovariectomy.

Ovariectomy and sham-operations in the younger age groups (5–15 days) caused a gradual increase in corticosterone concentration with maximal values 6 days after operation or later. The response of corticosterone secretion to these operations became more moderate and quicker, i.e. more adult-like, at 28 days of age, the age where corticosterone concentrations in intact rats also seemed to reach a plateau at an adult-like level. Corticosterone binding changed only marginally after ovariectomy or sham-operations until 28 days of age, when an increase was induced by these operations. After adrenalectomy or combined adrenalectomy/ovariectomy, however, marked increases in serum binding of corticosterone were always seen. In summary: though a parallel developmental pattern of serum corticosterone levels and corticosterone binding was seen in the maturing rat, interference with the normal condition causes divergent responses in these two parameters. Moreover, the responses vary with maturational age.

A complete analysis of the developmental pattern of concentrations of corticosterone in the blood of female rats is unavailable. Previous studies included data on only part of the period between birth and puberty (Bartova 1968; Ramaley 1972; Cote & Yasumura 1975) or presented data without regard to sex (Allen & Kendall 1967; Daniels et al. 1972; Henning 1978). Moreover, estimations were made by either fluorimetric methods (Gala & Westphal 1965; Levine et al. 1967; Bartova 1968; Ramaley 1972) or by competitive protein binding (Daniels et al. 1972; Cote & Yasumura 1975; Henning 1978), which two methods yielded different results especially for low levels.

Both in the adult and in the immature rat (Koch 1969; Westphal 1971b; Henning 1978; D’Agostino & Henning 1981) serum binding activities for corticosterone, essentially due to the corticosteroid binding globulin (CBG) (Slaunwhite et al. 1962; Savu et al. 1973), have been demonstrated. This CBG plays a role in the control of the physiological action of corticosterone, whereas its level fluctuates...
with changes in concentration of corticosteroids and under the influence of sex hormones (Westphal 1971c), the main regulatory factor of CBG synthesis being thyroidal function (Westphal 1971c; D'Agostino & Henning 1981).

Interactions between adrenal and gonadal function have been described (see Andrews 1977) and, more particularly, adrenal involvement in the process of sexual maturation of the female rat has been suggested (Ramaley 1974, 1976). It therefore seemed of interest to study, by radioimmunoassay and equilibrium dialysis respectively, corticosterone concentrations and corticosterone binding in intact rats as well as in rats that had been ovariectomized, adrenalectomized or both, during the course of sexual maturation.

Materials and Methods

Animals

Nine-hundred-eightyfive immature female rats of the R-Amsterdam strain (a Wistar sub-strain) were used. In these rats vaginal opening and first ovulation occurred at about 40 days of age at a body weight of 90–100 g (Meijs-Roelofs 1972). The rats were weaned at 22 days of age and kept under conditions of controlled temperature and light (light period 05.00–19.00 h). Standard dry food pellets and tap water were available ad libitum. Litter-mates were divided between experimental and control groups. Rats operated upon before weaning were kept with their mothers and those belonging to the different experimental groups were kept with separate mothers. Rats operated upon after weaning and belonging to the same treatment group were kept in one cage. For estimations in intact rats three groups were used at time intervals of several months.

Ovariectomy, adrenalectomy, the combined operation or sham-operation was performed between 10.00 and 12.00 h by bilateral approach under ether anaesthesia. At operation the rats were aged 5, 9, 15 or 28 days when their respective body weights were 10.6 ± 0.1 g (SEM; n = 153), 15.4 ± 0.2 g (n = 155), 24.9 ± 0.3 g (n = 116) or 52.3 ± 0.5 g (n = 86). In addition, one group of adult rats (n = 52), 3 months of age, was operated at metoestrus. Completeness of operations was always checked macroscopically at autopsy and in some cases also histologically. The rats were killed at 15.00 h 2, 4 or 6 days after operation. Blood of intact and operated rats was collected under light ether anaesthesia either by puncture of the ophthalmic venous plexus or, in rats aged 15 days or less, by decapitation. Anaesthesia and collection of blood were always performed within 3 min in order to avoid the influence of stress on the corticosterone concentration (Ramaley 1972). Blood was allowed to clot overnight in a refrigerator before centrifugation. The serum was separated and stored at –20°C. Serum of rats belonging to the same experimental group was pooled. Depending on the age of the group, the number of rats per pool was 4–27.

Corticosterone isolation and radioimmunoassay

Prior to assay, corticosterone was isolated as follows: ethyl acetate/cyclohexane (1:1, v/v) extracts from whole sera were applied to Sephadex LH20 (Pharmacia, Bois d'Arcy, France) columns (4 × 0.5 cm) equilibrated with benzene/ethanol (95:5, v/v). According to preliminary determinations with a [3H]-corticosterone tracer, the fraction containing corticosterone was eluted with 3.2 ml benzene ethanol (95:5, v/v). This eluate was submitted to thin layer chromatography (TLC) on a silica-gel F1500 plate (Carl Schleicher and Schüll, Socolab, Paris, France) in benzene/methanol/acetic acid (94:4:1, by vol). The zone with a Rf value corresponding to authentic corticosterone was extracted twice by ethyl acetate and twice by ethanol and finally filtered through LH20 micro-columns. The yield of the whole purification was about 80%, as measured with an incorporated corticosterone radioactive standard. In the final extracts corticosterone was estimated by radioimmunoassay; a specific anti-corticosterone-21-hemisuccinate-bovine serum albumin antibody, obtained in the rabbit (Institut Pasteur, Paris, France) was used: the % cross-reactivity for B/B0 = 0.5 was 100% with corticosterone, 7% with cortisol, 6.5% with progesterone and between 0.08 and 3% with oestrogens, aldosterone or androgens. At least two measurements were made for each pooled serum sample. The detection limit was 10 pg.

Blanks obtained from the solvents run through the whole extraction procedure were tested by radioimmunoassay; no interference with the specific antibody was seen.

Radio-inert corticosterone was purchased from Roussel-Uclaf (Romainville, France) and [1,2,6,7(n)3H]corticosterone (82 Ci/mmol; The Radiochemical Center, Amersham) of 99% checked purity was used. The samples were counted in an Intertechnique SL 30 scintillation spectrometer, with the internal standard technique for quenching evaluation, in 5 ml of Picofluor TM 30 (Packard Instruments, SA - Rungis, France).

Binding studies

The batch-wise gel equilibration technique of Pearlman & Crepy (1967), using a suspension of Sephadex G-25 as the semi-permeable membrane, was applied for measuring the binding of corticosterone in the sera. This method resembles in principle that of equilibrium dialysis, with the difference that equilibration is more rapid and conveniently attained with the gel technique. The data thus obtained represented mainly the binding activity of the serum CBG (Savu et al. 1973). They were expressed as 'C values' i.e. C = (Sb/Su) × (1/p) 1/2, in which Sb = bound steroid, Su = unbound steroid and p = protein

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concentration in g/l (Westphal 1971b). The C-values determinations involved a series of the test tubes containing a fixed amount of $^3$H-ligand (about 100 000 CPM i.e. $0.5 \times 10^{-9} \text{ m}$) and increasing amounts of protein. To ensure optimum sensitivity, accuracy and reproducibility of results, the protein concentrations were chosen so that Sb/Su values would fall within reasonable limits, i.e. not too distant from Sb/Su = 1. The binding values per liter of serum were calculated by multiplying the C value defined above by the protein concentrations of II serum (C/l). Results were similar with or without the removal of endogenous hormones; these were eliminated according to a conventional technique using activated charcoal (Savu et al 1977). Serum proteins were assayed according to Lowry et al. (1951).

**Statistical aspects**

The amount of blood needed for corticosterone assay and determination of corticosterone binding necessitated pooling of blood from rats of the various experimental groups, thereby eliminating standard statistical procedures. According to Westphal (1971a) analysis of serum pools is preferable to measurement of limited numbers of individual sera. Moreover, by studying non-operated rats in three series with intervals of several months and by studying the effects of surgical treatments after post-operational intervals of 2, 4 and 6 days, a clear indication of the reliability of the observed results could be obtained.

**Results**

**Serum levels of corticosterone and corticosterone binding**

Corticosterone concentrations during development as measured in three separate groups of female rats are shown in Fig. 1a. Though some variation was present between values obtained in the three groups, the general pattern was similar: from a value of ± 145 nM at birth a fall in corticosterone concentration was seen and lowest values (< 87 nM)

**Figs. 1a and b.**

a) Serum corticosterone concentrations and b) serum corticosterone binding expressed as C value per l in three groups (●, Δ, △) of immature female rats over the period of 0 to 34 days of age. Each point represents the mean of a duplicate measurement in pooled blood; blood was pooled from 9–27 rats at 0–7 days of age, from 6–8 rats at later ages. Line arbitrarily drawn.
were reached between 3 and 12 days of age. From then on corticosterone concentrations showed a continuous rise ending at about 28 days of age when a plateau (values between 580–725 nM) seemed to have been reached.

Corticosterone binding, expressed in C/l, in the blood of the same three groups of rats is shown in Fig. 1b. Apart from some variation between groups, a clear pattern was found again, with an initial C value at birth of 60–80, immediately followed by a drop towards minimal binding activity, present between 3 and 12 days of age. Thereafter a steep rise in binding activity was seen towards C values of 200 and higher at 28 days of age and thereafter.

When Fig. 1a and b are compared a clear parallelism between the development patterns of serum corticosterone concentration and serum corticosterone binding is seen from birth until about 28 days of age.

Effect of surgical treatments on serum levels of corticosterone

Results of ovariectomy, adrenalectomy, the combined operation, sham-ovariectomy and sham-adrenalectomy on the serum concentration of corticosterone are shown in Table 1. It may be seen that the effects of operation were generally comparable in ovariectomized, sham-ovariectomized and sham-adrenalectomized rats and on the other hand in adrenalectomized rats and in rats with combined adrenalectomy-ovariectomy.

There appeared to be an effect of ovariectomy, sham-ovariectomy and sham-adrenalectomy on the serum corticosterone concentration at all ages studied: operating at 5, 9 or 15 days of age a rise in corticosterone concentrations was found. Moreover, without exception, absolute values reached in these age groups were highest 6 days after operation. It may also be seen in all these groups that the higher the age at operation, the higher the absolute

Table 1.

Corticosterone concentrations* in control, in ovariectomized (Ovx), adrenalectomized (Adx), adrenalectomized-ovariectomized (Adx-ovx) and sham-operated rats 2, 4 and 6 days post-operatively.

<table>
<thead>
<tr>
<th>Age at operation (days)</th>
<th>Age at autopsy (days)</th>
<th>Corticosterone concentration (nM)</th>
</tr>
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* Values are means of four determinations, i.e. duplicate measurements on two series of pooled serum (6–12 rats per pool). Differences between duplicate values on the same pool were always inferior to 8%.
value in corticosterone concentration. When operations were carried out at 28 days of age, the situation was quite different: ovariectomy and sham-ovariectomy now caused a fall in corticosterone concentration, an effect which did not show a clear dependence on the interval after operation. In the case of sham-adrenalectomy a slight fall in corticosterone levels, as compared to values in intact rats, was seen at 2 days, but there was a rise at 4 and 6 days after operation.

In the apparently different condition of adrenalectomy and of combined adrenalectomy-ovariectomy, corticosterone concentration had clearly decreased 2, 4 and 6 days after operation, if the operation was performed at 15 or 28 days of age. However, removal of the adrenal gland at 5 or 9 days of age caused no consistent, clear decrease in corticosterone concentration. Adrenal-like tissue was not detected in these rats either macroscopically or histologically.

The experiment was repeated at 9 days of age in additional groups of rats; this time rats were allowed to live for 2, 6 or 10 days after adrenalectomy or combined adrenalectomy-ovariectomy; per group 6–8 rats were used. At 11, 15 and 19 days of age corticosterone levels were 15, 52 and 93 nM in adrenalectomized and 17, 40 and 61 nM in adrenalectomized-ovariectomized rats, compared to 23, 104 and 185 nM in their intact controls, indicating that, at these ages, removal of the adrenal glands caused a lasting fall in the level of corticosterone, although a considerable level remained.

Adrenalectomy performed on adult metoestrous rats resulted in corticosterone concentrations of 26, 38 and 116 nM 2, 4 and 6 days later; comparable data for adrenalectomized-ovariectomized rats were 35 nM after 2 days and less than 2.9 nM after 4 and 6 days; values in sham-ovariectomized rats were 609 nM at 2 days, 870 and 914 nM at 4 and 6 days after operation, whereas values in intact control rats were 957 ± 260 nM (n = 3).

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Table 2.

Corticosterone binding (C-value) in control, in ovariectomized (Ovx), adrenalectomized (Adx), adrenalectomized-ovariectomized (Adx-ovx) and sham-operated rats 2, 4 and 6 days post-operatively.

<table>
<thead>
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<th>Age at operation (days)</th>
<th>Age at autopsy (days)</th>
<th>Corticosterone binding (C-value: C/l)*</th>
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* See Materials and Methods. Values are means of four determinations, i.e. duplicate measurements on two series of pooled serum (6–12 rats per pool). Differences between duplicate values on the same pool were 5–10%.
Corticosterone concentration in ovariectomized (●), adrenalectomized (△), both adrenalectomized and ovariectomized (■), sham-ovariectomized (○) or sham-adrenalectomized (□) rats at 2, 4 and 6 days after operation; values expressed as % of the value in intact controls (= 100%). Arrows show when the operations were performed.

Effect of surgical treatments on serum levels of corticosterone binding

The effect of ovariectomy, sham-ovariectomy or sham-adrenalectomy on corticosterone binding appeared to be negligible in rats operated at 5 or 9 days of age (Table 2). A marginal decrease in corticosterone binding of rats operated at 15 days of age was found in ovariectomized and sham-ovariectomized rats, but no effect was seen at that age after sham-adrenalectomy. However, operation at 28 days of age provoked a marked increase in corticosterone binding of ovariectomized, sham-ovariectomized and sham-adrenalectomized rats.

As was found for corticosterone values, the effect on corticosterone binding of adrenalectomy or combined adrenalectomy-ovariectomy also seemed comparable in the two groups. At all ages studied a marked increase in corticosterone binding was seen...
Corticosterone binding (C/L) in ovariectomized (○), adrenalectomized (▲), both adrenalectomized and ovariectomized (▲), sham-ovariectomized (○) or sham-adrenalectomized (□) rats at 2, 4 and 6 days after operation; values expressed as % of the value in intact controls (= 100%). Arrows show when the operations were performed.

Changes in level of corticosterone and of corticosterone binding after surgical treatment expressed as percentages of control values.

Since, in developmental studies, effects of operations should be considered against a background of changing values in intact rats, it seemed of interest to express values after operation as a percentage of the values in intact rats of the same age (Figs. 2 and 3). The increase in corticosterone concentration induced by ovariectomy, sham-ovariectomy or sham-adrenalectomy at 5, 9 or 15 days of age (expressed as a percentage of the value in intact rats) was not higher at the older age. However, the maximal response to operation occurred earlier in
the group operated on day 15 than in groups operated on days 5 and 9. In the same groups the changes in binding of corticosterone appeared to be marginal (Fig. 3). Rats subjected to the same operations on day 28 showed first a slight decrease in corticosterone concentration (Fig. 2), which was somewhat reversed thereafter, whereas corticosterone binding tended to increase, especially in the ovariectomized group (Fig. 3).

In adrenalectomized and in adrenalectomized-ovariectomized groups a clear decrease in corticosterone concentration was only seen after operation at 15 or 28 days of age (Fig. 2). Corticosterone binding, however, clearly increased in all age groups. This response to the operation seemed to occur more quickly in the older rats (Fig. 3).

Discussion

Corticosterone levels in intact immature female rats as measured by radioimmunoassay in the present study are generally in good agreement, both in size and in developmental pattern with data obtained by others using protein binding assay (Daniels et al. 1972; Henning 1978) or colorimetric techniques (Koch et al. 1967). They are also comparable to values recently reported and obtained by radioimmunoassay (Miyabo et al. 1980). The present study extends available data by including both neonatal and late-prepubertal periods and by using exclusively female rats. This seems important, since Westphal (1971b) indicated that after 21 days of age differences exist in corticosterone concentration as well as in CBG activity in the blood of male and female rats.

The binding of corticosterone by whole sera corresponds essentially to the activity of CBG or transcortin. Influence of other serum proteins, i.e. albumin and α1-acid glycoprotein is negligible (Westphal 1971a; Savu et al. 1973).

The parallel rise in corticosterone concentration and corticosterone binding starting at about 12 days of age, after the parallel neonatal drop to very low levels, is in full agreement with the data of Henning (1978). In accordance with Westphal (1971a), Daniels et al. (1972) and Miyabo et al. (1980) we found that corticosterone concentrations continue to rise or at least remain high around 28 days of age, reaching a level similar to that of adults. In contrast, Henning (1978) using pooled blood of males and females, found a clear fall in corticosterone concentration at day 28. This could be explained by the fall in corticosterone levels which occurs in male rats at that age (Westphal 1971a). Another factor may be that Henning (1978) sampled blood at 11.00 h, whereas our samples were taken at 15.00 h, i.e. near the diurnal peak (Ottenweller et al. 1979). A circadian rhythm in corticosterone secretion has been shown to have developed by the end of week 4 of life (Ramaley 1972; Ulrich et al. 1976; Takahashi et al. 1979; Miyabo et al. 1980).

The effects of removal of ovaries and/or adrenals and of sham-operations on both corticosterone concentration and corticosterone binding were studied at three post-operative intervals. This approach was chosen to detect possible changes in both parameters, of which the time of occurrence was unpredictable. Indeed in the younger rats a relatively slow post-operative response was seen (see below). Effects obtained were generally comparable in ovariectomized sham-ovariectomized and sham-adrenalectomized rats and, on the other hand, in adrenalectomized and adrenalectomized-ovariectomized rats.

The effect of ovariectomy, sham-ovariectomy and sham-adrenalectomy on corticosterone concentration often showed a gradual increase of surprisingly long duration in the younger age groups, e.g. after sham-ovariectomy on day 9 corticosterone levels increased which response reached its maximum at or later than 6 days after operation.

Gala & Westphal (1965) reported a lack of effect 45 days after ovariectomy performed in the 12-day old rat. The present data show a clear and acute increase in corticosterone concentration during at least a 6-day period after ovariectomy performed at 5, 9 or 15 days of age. Both in absolute sense and when corticosterone concentrations are expressed as percentages of the values in intact rats, it becomes clear that in young rats of about 5–15 days of age ovariectomy and sham-operation are procedures which induce changes which last for several days, and which will be generally considered as 'stress' effects. The maximal response to such 'stresses' seemed to occur earlier after operating at 15 days than at 5 and 9 days of age. It seems possible that the neonatal decline in numbers of glucocorticoid receptors in the anterior pituitary, followed by an increase in number of these receptors and maturation of their way of functioning around 10 days of age (Sakly & Koch 1981) play a role in the responses observed by us. Occurrence of
a 'refractory' period of the hypothalamic-hypophysial-adrenal system, from 3–15 days of age (Allen & Kendall 1967; Levine 1970) could, therefore, not be confirmed in the present study. Others (Zarrow et al. 1968; Koch 1969) have already suggested that this 'refractoriness' is largely dependent on the nature and intensity of the stress and perhaps even on the sensitivity of the corticosterone assay used (Schoenfeld et al. 1980).

At 28 days of age the effects of ovariectomy as well as sham-operation were totally different and quantitatively quite moderate: as in the adult metoestrous rat a slight decrease in corticosterone level was observed 2 days after operation, but levels returned to normal at 4 and 6 days after operation. Thus, in the female rat at 28 days of age, the reaction pattern of corticosterone secretion to operational stress seems to become similar to that found in adults.

The effects of adrenalectomy and of combined adrenalectomy-ovariectomy were also clearly dependent on the age at operation. It is notable that operating 5-day old rats corticosterone concentrations were not lowered at 6 days after operation; after the combined operation performed on day 9 of life, considerable corticosterone concentrations were still found 10 days later. By contrast, in 15- and 28-day old as well as in adult rats an important decrease in corticosterone concentration was induced by adrenalectomy with or without ovariectomy. Only in the adult rat, at 4 and 6 days after the combined operation, was complete disappearance of corticosterone from the blood seen. These data suggest that in immature rats accessory tissue exists which is capable of corticoid production. Existence of accessory adrenal tissue has been suggested by several authors (Wyman 1928; Parkes 1945; Soffer et al. 1961; Tait & Tait 1979); our attempt to detect any such tissue histologically in our adrenalectomized rats failed.

The high increase in corticosterone binding occurring after adrenalectomy, with or without ovariectomy, is in agreement with findings of Westphal (1971b,c) in mature rats, where, however, the increase in corticosterone binding occurred concomitantly with a decrease in total corticosterone concentration. In the present study in the immature rat this increase in corticosterone binding was found while little or no decrease in corticosterone concentration occurred after adrenalectomy. Since CBG secretion is controlled not by adrenocorticotropic hormone but mainly by thyroidal activity, both in the mature (Westphal 1971c) and in the immature rat (D'Agostino & Henning 1981), these findings are not too surprising. They indicate that in the immature rat an adrenal-linked factor different from the level of corticosterone acts as a signal for thyroid action on CBG synthesis. The general conclusion is warranted that in the intact immature rat a parallel development in corticosterone secretion and corticosterone binding occurs. Interference with the normal condition causes responses of corticosterone concentration and corticosterone binding that may be highly divergent and which may vary with maturational age. Further studies are needed to clarify the physiological significance of these findings.

Acknowledgments

This work was supported by grants from DGRST (78.7.27.38), INSERM (77.4.213.4) and the Fondation Pour La Recherche Medicale. We are grateful to Dr. F. Dray and Mrs. S. Mamas (Institut Pasteur-Paris) for their generous gift of corticosterone antisera.

The skillful technical assistance of Michèle Maya is acknowledged. We wish to thank Dr. J. Moll for his criticism of the manuscript and Mr. G. Ketting for animal care and breeding.

References


Received on December 24th, 1981.