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Metabolism of exogenous cortisol in the rat in various experimental conditions

Cortisol is one of several steroids known to be metabolized by liver microsomal enzymes. The ability to metabolize drugs is lower in very young and old animals (Kato, Vassanelli & others, 1964; Catz & Yaffe, 1967; Kalser, Forbes & Kunig, 1969) and is modified by some drugs like the barbiturates (Conney, 1967). There is also a diurnal rhythm in the activity and metabolism of drugs (Scheving, Vedral & Pauly, 1968; Radzialowski & Bousquet, 1968; Szeberenyi, Szalay & Garattini, 1969).

We now report the half-life of cortisol in the plasma of rats under several experimental conditions. Sprague-Dawley rats of either sex, 150–200 g, were used. The infant rats were 12–14 day old and weighed 45 ± 5 g. The animals were housed at constant temperature (22°) and humidity (60%) in groups of 4–5 animals per cage and kept on a standard diet (Alal 56, Milan). Cortisol hemisuccinate (kindly supplied by Ormonoterapia Richter, Milan) at a dose of 5 or 10 mg of cortisol/kg in 2 ml saline was injected into the tail vein of the animals which were then killed at different times by incision of the carotid arteries. Plasma was collected and tested for cortisol. Experiments were usually made in the morning.

Corticosterone was estimated spectrofluorimetrically (Guillemin, Clayton & others, 1959) and cortisol by the method of Stockham (1963). The daily variations observed in the endogenous corticosterone plasma concentrations of male and female rats are shown in Fig. 1. There is a diurnal rhythm with a fall in the morning and the highest values in the late afternoon.

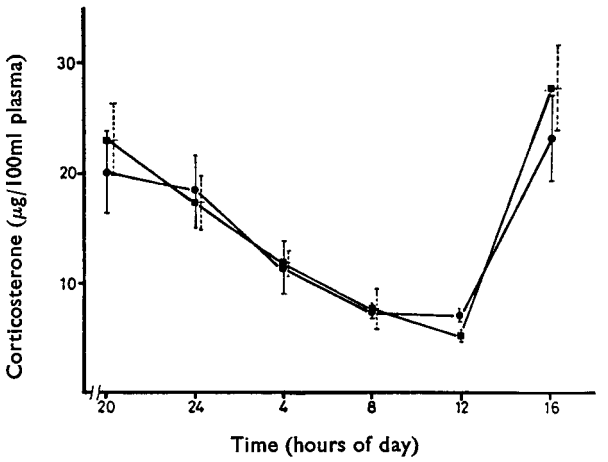

FIG. 1. Mean plasma levels of corticosterone in rats (145 ± 10 g) during the day. ■ --- ■ female, ● — ● male rats.

The rate of disappearance of cortisol from plasma after an intravenous administration of 5 mg/kg at different times during the day is given in Table 1 for values at 9 a.m. and at 9 p.m. in animals previously fasted for 12 h. The half-life of cortisol in the evening is greater. Similar differences were obtained using animals fed *ad libitum*.

Table 1. *Plasma half-life of exogenous cortisol in several experimental conditions*

Treatment or experimental condition	Sex	Weight (g)	Dose of cortisol (mg/kg, i.v.)	Plasma half-life (min)	Significance *P*
Diurnal variation					
9 a.m.	Female	145 ± 10	5	10·7	<0·02
9 p.m.	„	145 ± 10	5	16·4	
Age: Infant	Male	45 ± 5	10	20·4	<0·001
Adult	„	180 ± 10	10	12·4	
Phenobarbitone acute ..	„	200 ± 20	5	10·4	<0·05
Saline acute	„	200 ± 20	5	20·2	
Phenobarbitone chronic	„	220 ± 20	5	9·0	<0·02
Saline chronic	„	220 ± 20	5	14·4	

Table 1 also shows the disappearance of intravenously given cortisol (10 mg/kg) from plasma of male young rats and infant rats. The disappearance of cortisol is more rapid in the young adult than in the infant rats. It also gives the results after an acute pretreatment of the animals with phenobarbitone (72 mg/kg, i.p.), 24–48 h before the injection of cortisol. Different slopes are evident after 24 h, but the most marked differences are after 48 h. In the chronic experiment, animals were treated with phenobarbitone (37·5 mg/kg, i.p.) twice a day for 6 days; 48 h after the last pretreatment they received cortisol. The half life in the plasma of cortisol in phenobarbitone-treated animals is significantly less than in controls (Table 1).

The daily variations in the endogenous levels of plasma corticosterone have been extensively studied and our data are in general agreement with those in the literature. According to Guillemin, Dear & Liebelt (1959) the peak in the adrenocortical secretion in the albino rat occurs at about 6 p.m. and it would reflect changes in the ACTH secretion by the pituitary (Perkoff, Eik-Nes & others, 1959; Galicich, Halberg & others, 1965).

Our experiments also show differences in the disappearance rate of injected cortisol at different times of the day. Concomitant with high endogenous corticosterone levels, the half-life of exogenous cortisol is longer. This would agree with the results of Radzialowski & Bousquet (1968) who showed a daily rhythm in hepatic drug-metabolizing enzymes in the rat and mouse that was abolished by adrenalectomy or by constant levels of plasma corticosterone. These results are further supported in man by our unpublished findings has exogenous cortisol that a longer half-life in the morning than in the afternoon. Thus, there appears to be a relation between the activity of the pituitary-adrenal axis and the activity of drug-metabolizing enzymes.

In early infancy, pituitary function is not well developed and the fluctuations in the level of plasma corticosterone are much less evident (Jailer, 1950; Schapiro, Geller & Eiduson, 1962; Leeman, 1963; Allen & Kendall, 1967). Drugs degraded by microsomal enzymes show a lower rate of metabolism at this time (Kato & others, 1964). We found in infant rats that the disappearance of intravenous cortisol is slower by comparison with that in adults and this difference is highly significant ($P < 0{\cdot}001$).

Steroid hormones are supposed to be endogenous substrates for drug-metabolizing enzymes present in liver microsomes, and substances stimulating the microsomal hydroxylation of drugs also stimulate the microsomal hydroxylation of steroids (Kuntzman, Jacobson & others, 1964). This is evident from the data of Conney, Jacobson & others (1965) who reported an altered cortisol metabolism after pre-treatment of guinea-pigs with phenobarbitone, with a major excretion of the 6-β-hydroxy-component. This correlates with the increased urinary output of the polar metabolite found in man after phenobarbitone by Werk, MacGee & Sholiton (1964) and Burstein & Klaiber (1965).

Recently, we have also found (unpublished) exogenous cortisol to have a faster disappearance rate in man after chronic treatment with phenobarbitone. Our results with animals agree with the above findings.

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