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Effect of Metopirone on the rate of cortisol disappearance from plasma

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METOPIRONE® (2-methyl-1,2-*bis*(3-pyridyl)-1-propanone SU 4885) is a drug used for testing the pituitary-adrenal function because of its capacity to block adrenal 11-β-hydroxylase.[1] Recent studies have also demonstrated that Metopirone is an inhibitor of liver microsomal enzymes responsible for *O*-demethylation, *N*-demethylation and phenyl ring hydroxylation.[2] Since it is known that cortisol is also metabolized by liver microsomal enzymes it was of interest to investigate if Metopirone was able to affect not only biosynthesis but also the rate of disappearance of cortisol from plasma.

For the estimation of the half life of cortisol in plasma 6·7 mg/kg of cortisol hemisuccinate were injected into the tail vein of 200 ± 10 g male Sprague–Dawley rats (103 animals in all were used). At different times (5–45 min) after the injection the animals were decapitated and the plasma cortisol concentration was determined spectrofluorimetrically according to the method of Jansen *et al.*[3] The plasma samples were extracted with dichlormetane and the separation of cortisol from the endogenous corticosterone was achieved by two extractions with carbon tetrachloride. With this procedure the fluorescence in plasma of i.v. saline injected rats corresponded to a maximum of 5 μg corticosterone/100 ml. Some experiments were repeated also with paper chromatographic determination of cortisol.[4] Results obtained with this method are not given in detail because they were in substantial agreement with the finding obtained by using the Jansen method. The concentration of cortisol expressed in μg/100 ml of plasma were plotted against time. Regression lines from the plasma half-life of cortisol were determined according to the method of least squares. Extrapolation of the line to $t = 0$ permitted to establish an apparent volume of distribution.

Metopirone was given at doses of 50–200 mg/kg i.p. 1 hr before the cortisol administration. Suitable controls established that Metopirone and its metabolite [2 methyl-1,2-*bis* (3 pyridyl)-1-propanol, SU 5236] did not interfere with the determination of cortisol.

The plasma levels of exogenous cortisol declined exponentially with a $t\frac{1}{2}$ of 16·6 min [see Fig. 1(a)], a value corresponding to the data of recent literature.[5–7]

The administration of Metopirone at the dose of 50 mg/kg did not change the disappearance of cortisol from plasma [see Fig. 1(b)], 150 mg/kg of Metopirone caused a lower rate of disappearance, $t\frac{1}{2} = 34{\cdot}5$ min [see Fig. 1(c)]. The plasma cortisol level remained almost unchanged up to 45 min [see Fig. 1(d)] if the dose of Metopirone was 200 mg/kg, indicating that the $t\frac{1}{2}$ must have been longer than 45 min. The apparent distribution volume of cortisol was not significantly changed in the treated animals.

The results of the present study indicate that a single acute administration of Metopirone decreases the rate of disappearance of cortisol from the plasma of rats.

Earlier data have shown that Metopirone inhibits not only steroid 11-β-hydroxylase but also C-18- and C-19-hydroxylations.[8–10] Furthermore it inhibits the oxidation of fatty acids and sterols in liver mitochondria.[11]

Our experiments suggest that Metopirone inhibits the liver enzyme system(s) responsible for inactivation of adrenal steroids.

This hypothesis is not in contrast with previous observations showing that Metopirone increases the activity of hepatic microsomal oxidases[12] because it is known that the same drug depending upon the experimental conditions may block or enhance (induce) the same microsomal enzyme.[13, 14] The finding that Metopirone may affect adrenal steroid metabolism may have significance in the evaluation of "Metopirone test".

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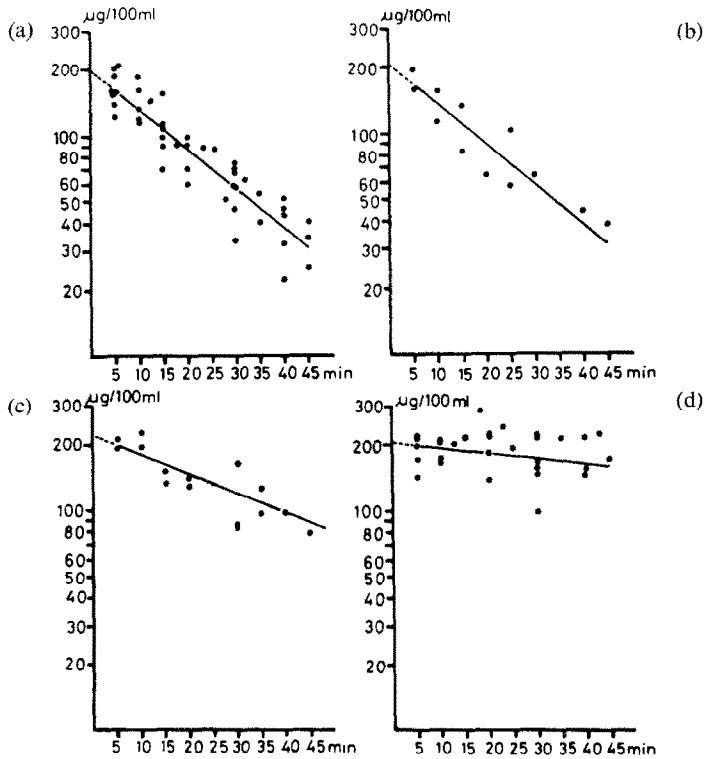

FIG. 1. Level of plasma cortisol (logarithm scale) in μg/100 ml obtained at different times following administration of cortisol hemisuccinate (6·7 mg/kg i.v.) in rats treated 1 hr before with saline (a) or Metopirone 50 mg/kg ip. (b) 150 mg/kg i.p. (c) 200 mg/kg i.p. (d).

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