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BIOLOGY

An Inhibitor of Adrenal Steroid 11β-Hydroxylase

Trans-1,4-*bis* (2-chlorobenzylaminomethyl) *cyclo*hexane dihydrochloride ('AY–9944')[1] has been shown to represent a novel class of cholesterol biosynthesis inhibitors which act by interfering with the enzymatic conversion of 7-dehydrocholesterol to cholesterol[2,3]. In laboratory animals, 'AY–9944' significantly depressed serum sterol-levels[4]. In view of its potential use as antihypercholesterolemic agent[5], we have studied the effects of this agent on adrenal steroid metabolism. The inhibition of 11β-hydroxylase by 'AY–9944' in rat adrenal homogenates is reported herewith.

The effect of 'AY–9944' on the conversion of progesterone, 11β-hydroxyprogesterone and 11-deoxycorticosterone to corticosterone by rat adrenal homogenates[6] was determined by the fluorometric method of Guillemenin *et al.*[7]. As indicated in Table 1, 'AY–9944' inhibited the conversion to corticosterone of both progesterone and 11-deoxycorticosterone without affecting that of 11β-hydroxyprogesterone respectively. Hence, in rat adrenal homogenates 'AY–9944' depresses 11β-hydroxylation without affecting 21-hydroxylation. The inhibitory action of the agent on 11β-hydroxylase was corroborated by measuring its effect on the conversion of 11-deoxycorticosterone-4-^{14}C to corticosterone-4-^{14}C by rat adrenal homogenates; at a final concentration of 1×10^{-4} M the inhibition was 60 per cent.

The effect of 'AY–9944' on 11β-hydroxylation was compared with that of 'SU–4885' ('Metopirone'), a known 11β-hydroxylase inhibitor[8] (Fig. 1). The concentration of

Table 1. Effect of 'AY-9944'* on the Conversion of Progesterone, 11-Deoxycorticosterone and 11β-Hydroxyprogesterone to Corticosterone by Rat Adrenal Homogenates

Substrate	Inhibition of corticosterone formation (%)†
Progesterone	73
11-Deoxycorticosterone	63
11β-Hydroxyprogesterone‡	2

* 1×10^{-4} M final concentration.
† Each value is the mean of three separate determinations.
‡ Final concentration, 1×10^{-3} M 'AY-9944'.

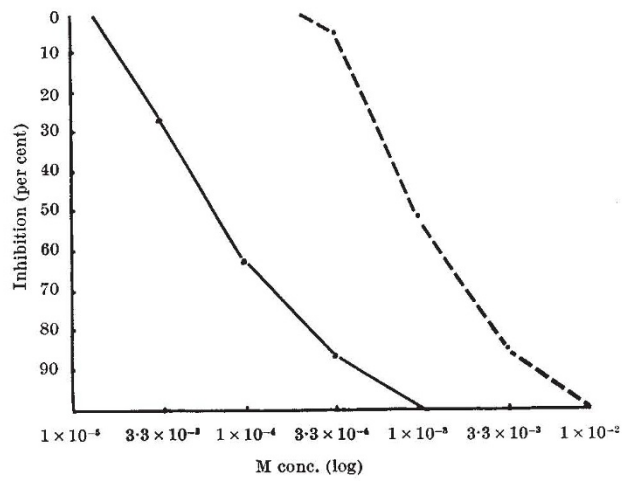

Fig. 1. Effects of 'AY-9944' (——) and 'SU-4885' (– – –) on the conversion of 11-deoxycorticosterone to corticosterone by rat adrenal homogenates

'AY–9944' sufficient to cause a 50 per cent inhibition of 11β-hydroxylation, that is, $6{\cdot}6 \times 10^{-5}$ M, was significantly lower than that of 'SU–4885', that is, $9{\cdot}6 \times 10^{-4}$ M.

It is interesting to note that 11β-hydroxylase activity was not affected in adrenal homogenates obtained from rats given orally 10 μmole/kg of 'AY–9944'. In contrast, in liver homogenates obtained from the same animals the metabolism of 7-dehydrocholesterol, as measured by the method of Kandutsch[3,9], was completely blocked. The finding that, *in vivo*, 'AY–9944' does not affect rat adrenal 11β-hydroxylase parallels the experience with 'SU–4885' which, *in vivo*, was inactive in rats[10] and an effective 11β-hydroxylase inhibitor in dog[11] and man[8].

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Variations in Flow of Blood within the Epididymis and Testis of the Sheep and Rat

The total venous outflow from the testis and epididymis of conscious rams has been measured using the Fick principle with tritiated water as the dilution substance[1]. Because of their different functions the two organs might have quite different blood flows, and it cannot be assumed that each contributed blood to the total venous outflow in proportion to its weight. The technique of Sapirstein[2] has