$^{14}C$ in aliquots of the various fractions was performed in a Packard Tricarb spectrometer 3004[6].

The fraction of free steroids, obtained from 91 ml of duodenal juice contained 18,304 dpm $^{14}C$ and 3,789 dpm $^{3}H$. After separation into individual steroids a total of 17,526 dpm $^{14}C$ and 3,691 dpm $^{3}H$ could be detected in the 3 different compounds, of which DHEA represented 95.5% and 65.2% respectively. In addition to DHEA 2 unknown 17-ketosteroids with practically no $^{14}C$-activity were isolated from the fraction of free steroids. In the very non-polar compound (Rf in system A = 0.86, in system B = 0.53 (androst-4-ene-3,17-dione: 0.80 and 0.47) 14.2% of $^{3}H$-activity were found, as compared with 20.6% in the compound more polar than DHEA (Rf in system A = 0.19, in system B = 0.14 (DHEA: 0.48 and 0.32)). The fraction of steroid sulphates with 429,000 dpm $^{3}H$ in contrast consisted exclusively (98.1%) of DHEA sulphate.

From the recovery of merely 3.54% of administered free 4-$^{14}C$-DHEA the hydrolysis of 7$\alpha$-$^{3}H$-DHEA sulphate was calculated to have reached 9.89%. The rapid disappearance of free 4-$^{14}C$-DHEA and liberated 7$\alpha$-$^{3}H$-DHEA, probably due to immediate reabsorption from the duodenum (or the stomach?) is in agreement with previous findings[7]. Conversely, the reabsorption of DHEA sulphate proceeded very slowly, as indicated by a 40.93% recovery of $^{3}H$-activity, thus leaving ample time for acid hydrolysis of DHEA sulphate in the stomach. Furthermore, in view of the collection of 91 ml duodenal juice during 45 min corresponding to 2–3 l/24 h (2–4 l/24 h in normal adults) the sampling may be considered sufficiently complete in order to exclude major losses of steroids through the intestinal passage. Since it can be assumed that the remaining portion of DHEA sulphate is exposed to hydrochloric acid in gastric juice for an additional period of time, the 10% hydrolysis, observed over 45 min, may actually represent a minimum. The isolation of 2 unknown 17-ketosteroids from the fraction of $^{3}H$-labelled free steroids reflects the well-known formation of artefacts during acid hydrolysis of DHEA sulphate[8]. Whereas the non-polar compound exhibited chromatographic properties similar to those of androsta-3,5-diene-17-one, the identity of the more polar material could not as yet be established. No 17-ketosteroid resembling 3$\beta$-chloro-androst-5-ene-17-one could be detected.

*Zusammenfassung.* Nach oraler Gabe von 4-$^{14}C$-DHEA und Na-7$\alpha$-$^{3}H$-DHEA-sulfat liessen sich mittels einer Duodenalsonde 91 ml Duodenalsaft innerhalb von 45 min gewinnen, aus denen man u.a. $^{3}H$-markierte, freie 17-Ketosteroide isolierte. Anhand der Ausbeute an 4-$^{14}C$-DHEA konnte eine zumindest 10% betragende Hydrolyse verabreichten DHEA-sulfats nachgewiesen werden.

G. W. OERTEL and P. KNAPSTEIN

*Abteilung für Experimentelle Endokrinologie Universitäts-Frauenklinik, 65 Mainz (Germany),*
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## Adrenocorticotropic Effect in Humans of a Synthetic $\beta^{1-24}$ Corticotrophine Derivative

Synthetic $\beta^{1-24}$ corticotrophine, consisting of the first 24 amino acids of $\beta^{1-39}$ corticotrophine, possesses the full biological activity[1]. The adrenocorticotropic effect of $\beta^{1-24}$ corticotrophine can be enhanced by replacement of certain amino acids[2]. A derivative of $\beta^{1-25}$ corticotrophine, synthesized by BOISSONAS et al. is more active in humans blocked by dexamethasone than $\beta^{1-24}$ corticotrophine[3,4].

We investigated the steroidogenic potency of a new peptide related to $\beta^{1-24}$ corticotrophine, which has been synthesized by TESSER and SCHWYZER[5,6]. In D-serine$^{1}$-17,18 diornithine corticotrophine 1-24 tetracosactid, the arginine residues 17 and 18 are replaced by ornithine. Furthermore L-serine$^{1}$ is replaced by D-serine$^{1}$. It has been shown that this derivative has a more potent action in animals than $\beta^{1-24}$ corticotrophine[7]. The increase of the secretion of corticosterone into the adrenal vein of hypophysectomized rats is 10 times higher with a 4-fold prolonged effect.

*Methods.* $\beta^{1-24}$ corticotrophine tetracosactide, subsequently named 30920-Ba, and D-serine$^{1}$-17,18 diornithine $\beta^{1-24}$ corticotrophine tetracosactide, subsequently named 40401-Ba, were injected into healthy volunteers or patients without evidence of endocrinopathy, which were not blocked by dexamethasone. In crossover experiments all of them received the ACTH preparations within 1 week at the same dose level of 1 mg or 2 mg i.m. All experiments were started at 07.30. The urinary 17-hydroxycorticoids (HOC) were analysed by the method of LIDDLE et al.[8]. The plasma 11-hydroxycorticoids were measured with a modified method of MATTINGLY, the whole procedure being carried out at constant temperature of 25 °C[9].

*Results.* The effect of 2 mg 30920-Ba and 2 mg 40401-Ba on the urinary excretion of 17-hydroxycorticoids is shown in Figure 1. Measuring the 24 h excretion in 12 persons, there is a rise from 5.5 $\pm$ 0.75 mg to 8.0 $\pm$ 1.4 mg after 30920-Ba. Following the administration of 40401-Ba, the 17-hydroxycorticoids in urine increase from 6.4 $\pm$ 0.7 mg to 18.9 $\pm$ 3.7 mg. The difference of the values before and

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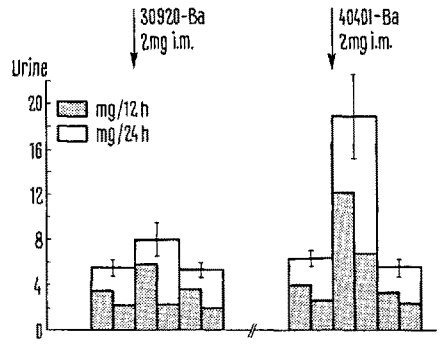


Fig. 1. Urinary excretion of 17-hydroxycorticoids (HOC) following injection of 2 mg 30920-Ba and 40401-Ba. Dark columns 17-HOC mg/12 h, empty columns 17-HOC mg/24 h.

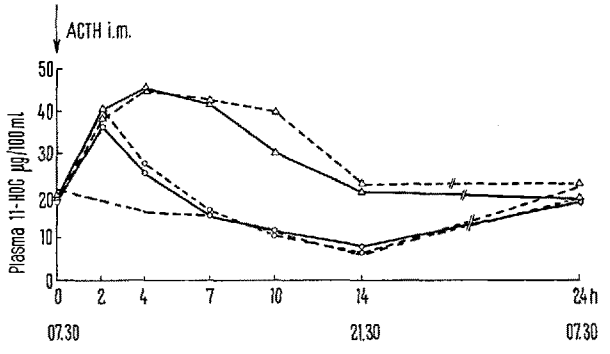


Fig. 2. Mean values of plasma 11-hydroxycorticoids (HOC) following injection of 1 mg or 2 mg 30920-Ba and 40401-Ba with regard to normal diurnal variation. o——o 1 mg 30920-Ba, o----o 2 mg 30920-Ba, △——△ 1 mg 40401-Ba, △----△ 2 mg 40401-Ba, ---- spontaneous diurnal variation.

Plasma-11-hydroxycorticoids after i.m. injection of synthetic ACTH derivatives at 07.30.

| | 1 mg 30920-Ba | 2 mg 30920-Ba | 1 mg 40401-Ba | 2 mg 40401-Ba |
|---|---|---|---|---|
| 0 h | 18.8 ± 3.3 | 18.8 ± 1.3 | 20.2 ± 2.6 | 19.4 ± 2.3 |
| 2 h | 36.5 ± 1.5 | 40.3 ± 9.0 | 40.5 ± 4.1 | 38.3 ± 5.3 |
| 4 h | 25.3 ± 1.4 | 27.8 ± 4.5 | 45.6 ± 1.7 | 45.0 ± 5.2 |
| 7 h | 15.5 ± 0 | 16.6 ± 2.3 | 42.0 ± 2.5 | 43.1 ± 9.4 |
| 10 h | 11.8 ± 0.25 | 10.8 ± 1.9 | 30.1 ± 5.9 | 39.9 ± 14.8 |
| 14 h | 8.0 ± 0.16 | 6.5 ± 1.1 | 20.9 ± 6.2 | 22.8 ± 20.0 |
| 24 h | 18.8 ± 3.5 | 19.3 ± 1.8 | 19.6 ± 1.3 | 23.2 ± 3.8 |

Mean values and standard deviation in µg/100 ml.

after stimulation is 2.4 mg for 30920-Ba and 12.5 mg for 40401-Ba, indicating that the increase produced by the synthetic derivative is 5 times higher. With regard to spontaneous diurnal variation, measured in 12 h urine specimens, the rise of the excretion of 17-hydroxycorticoids can only be observed in the first 12 h period after 30920-Ba, whereas after 40401-Ba it lasts for 24 h.

The determination of plasma 11-hydroxycorticoids gives more information on the dynamic of adrenal stimulation. In the Table the mean values and standard deviation of the mean of the 2 groups at dose levels of 1 mg and 2 mg of both derivatives are plotted. The group consisted of 5 and 8 persons respectively. It can be seen that the increase after both preparations is the same during the first 2 h. The effect of the synthetic derivative, however, lasts for more than 14 h after injection. The only difference between the 2 dose levels of 40401-Ba is that after 2 mg the standard deviation of the mean is greater, due to individual differences. It has to be noted that already 7 h after the injection of 30920-Ba the values of plasma 11-hydroxycorticoids follow the normal diurnal rhythm of the adrenals.

The curve of all mean values of the plasma 11-hydroxycorticoids is shown in Figure 2. The difference between the 2 derivatives is the same, independent of the 2 dose levels. The calculation of the area by planimetry using normal diurnal variation as baseline, gives for 1 mg 40401-Ba an area which is 4.8 times larger and for 2 mg 40401-Ba an area which is 4.5 times larger than the corresponding values of 30920-Ba.

In conclusion we may state that replacement of L-serine[1] by D-serine[1] and arginine 17,18 by ornithine 17,18 enhances the adrenocorticotropic effect not only in animals but also in humans. The synthetic derivative is about 5 times more active. The effect is probably due to a different enzymatic degradation.

*Zusammenfassung.* Am Menschen wurde die adrenocorticotrope Wirkung von $\beta^{1-24}$ Corticotrophin Tetracosactid und D-Serin[1]-17,18 Diornithin $\beta^{1-24}$ Corticotrophin nach i.m. Injektion untersucht. Das synthetische Derivat erwies sich als etwa fünfmal stärker wirksam als das natürliche Tetracosactid, hauptsächlich durch eine Verlängerung der Wirkungsdauer.

A. Walser and Th. Müller

*Medical Clinic and Medical Outpatient Clinic, University of Basel and St. Clara Hospital, Basel (Switzerland), 10 October 1967.*

## Mechanism of Non-Disjunction of Meiotic Chromosomes and of Degeneration of Maturation Spindles in Eggs Affected by Intrafollicular Overripeness[1]

Non-disjunction of meiotic chromosomes is thought to be the cause of various types of trisomy and monosomy. Principal etiological factors for the non-disjunction during ovogenesis which have been postulated are (1) post-ovulatory overripeness of normally ovulated eggs[2,3], (2) preovulatory overripeness of normally matured primary ovocytes[3-6], (3) perhaps chronological ageing of ovocytes during the growth period which may occur in aged mothers.

[1] The author wishes to express his thanks to Prof. E. Witschi, the Population Council, Bio-Medical Division, the Rockefeller University, for critical reading of the manuscript. This study was supported by the Ford Foundation Population Program, Grant No. 64-411.

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