Die hier aufgestellte Beziehung kann als Methode zur Bestimmung der Anpassungsfähigkeit empfohlen werden. Sie ist nur unter streng definierten und standardisierten Bedingungen für einen Tierstamm, konstante Umgebungstemperatur, Standarddiät, gleiche Anzahl Tiere im Kasten und Grösse der Bodenfläche pro Tier verwendbar. Trainierte Tiere, die in Käfigen mit Laufrädern untergebracht sind, zeigen keinen oder nur einen kurzfristigen, geringen Gewichtsverlust nach Übergang in die Höhe[11]. Bisher haben wir dort die strenge altersabhängige Gewichtsabnahme nicht nachweisen können. Schon aus anderen Untersuchungen[1,4,5] ist bekannt, dass Tiere in grösseren Höhen als 4000 m, auch wenn sie jung sind, stark in der Entwicklung zurückbleiben und das ursprüngliche Körpergewicht nicht wieder aufholen können. Die Höhe zwischen 3450 m und 3800 m[2] stellt hier eine obere Höhengrenze dar, oberhalb der das Leistungsniveau im Tal wohl nie erreicht werden kann.

Summary. Rats, kept in cages, show a transitory weight loss after exposure to high altitude, due to a reduced food intake. The measurement of the extent and the duration of the weight loss before the weight prior to exposure is regained can be used for the determination of the adaptability. The results of measurements at 3,450 m show that the adaptability decreases with age.

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Stimulation of the in vitro Biosynthesis of Corticosteroids by Angiotensin II

Previous studies on the effect of angiotensin II upon corticosteroid biosynthesis in vitro have produced conflicting results. Using relatively high doses (10 μg/g tissue) Kaplan and Bartter[1] observed a stimulating effect of angiotensin II on the formation of aldosterone, corticosterone and cortisol from endogenous precursors in slices of bovine adrenal cortex. Adding lower doses (0.1–1 μg/g tissue) Kaplan[2] found a more specific stimulation of aldosterone and corticosterone synthesis. Other authors, using rat[3,4], chicken[5] and dog[6] adrenals, reported angiotensin II to be ineffective.

In our experiments the effect of angiotensin II on the biological transformation of 1-C^{14}-Na-acetate, 4-C^{14}-cholesterol and 4-C^{14}-progesterone into C^{14}-labelled corticosteroids by cortex slices of fresh bovine adrenals were studied.

After 2 preincubation periods of 30 and 15 min, each followed by replacement of the medium, 1 g tissue was incubated in 10 ml Krebs-Ringer bicarbonate-glucose solution with 24 μCi (250 μg) 1-C^{14}-Na-acetate, 1.6 μCi (150 μg) 4-C^{14}-cholesterol or 1.6 μCi (150 μg) 4-C^{14}-progesterone under a continuous stream of 95% O_2 + 5% CO_2 at 37 °C for 120 min. 10 μg angiotensin II ('Hypertensin', CIBA) were added at the beginning and every 10 min throughout the 120 min incubation. Each experiment consisted of 5 samples with and 5 controls without angiotensin II. From tissue + medium progesterone (P), cortexone (DOC), corticosterone (B), 11-dehydrocorticosterone (A), aldosterone (ALD), 17α-OH-progesterone (OH-P), 17α-OH-cortexone (S), cortisol (F) and cortisone (E) were isolated by several paper chromatographic runs. The fractions of precursor radioactivity incorporated into these steroids were measured. Losses of C^{14}-radioactivity were checked by the recoveries of H^3-labelled trace amounts of the examined steroids added to the samples after incubation. The methods used have been elsewhere described in detail[7].

In control experiments, testing the sensitivity of the biosynthesis model to corticotrophic stimuli, ACTH ('Cortrophine', ORGANON; 8 IU/g tissue) enhanced significantly the conversion of 4-C^{14}-cholesterol to 4-C^{14} B, -F, -E and -ALD[8] and the formation of C^{14}-labelled DOC, B, A, S, F, and E from 1-C^{14}-acetate.

Angiotensin II was found to have no effects on the transformation of 4-C^{14}-progesterone and 4-C^{14}-cholesterol into 4-C^{14}-corticosteroids[9]. It stimulated, however, the synthesis of both C^{14}-17-desoxycorticosteroids and C^{14}-17α-OH-corticosteroids when 1-C^{14}-acetate was used as precursor, while the incorporation of radioactivity into P and OH-P decreased below control values. Obviously the effects of angiotensin II on 17-desoxycorticosteroid synthesis depended on the individual responsiveness of the adrenocortical preparation, which in turn is influenced by the premortal state of the individual animal[10] (salt and water balance, nervous stress). When the basal production (control) of 17-desoxycorticosteroids was low (upper part of Figure), angiotensin II enhanced the formation of B, A and ALD considerably; when the basal production was relatively high (lower part of Figure), these effects were much smaller.

The data confirm the findings of Kaplan and Bartter[1] that (1) angiotensin II acts directly upon the adrenal cortex, (2) high doses of the octapeptide stimulate the formation of both mineralo- and glucocorticosteroids.

Considering the fact that angiotensin II did not influence the transformation of 4-C^{14}-progesterone and 4-C^{14}-cholesterol and stimulated the incorporation of 1-C^{14}-acetate into corticosteroids, it can be assumed that angiotensin II stimulates steroid synthesis prior to cholesterol formation or activates a reaction(s) of a synthesis path-

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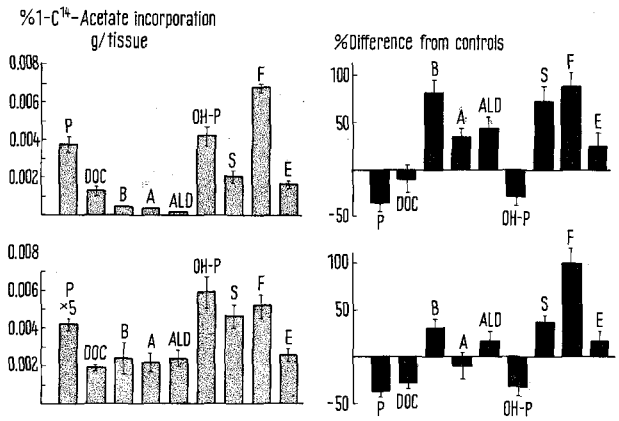
way(s) excluding free cholesterol and progesterone as intermediates. Therefore the site of action of angiotensin seems to be different from that of ACTH, which is supposed to act between cholesterol and pregnenolone[8,11,12].



Incorporation of 1-C^{14}-Na-acetate into corticosteroids and effects of angiotensin II (± S.E.M.).

Zusammenfassung. In Rindenschnitten frischer Rindernebennieren stimulierte Angiotensin II den Einbau von 1-C^{14}-Acetat in Mineralo- und Glukocorticosteroide, hatte jedoch keinen Effekt auf die Transformation von 4-C^{14}-Cholesterin und 4-C^{14}-Progesteron. Der Angriffspunkt des Angiotensins scheint danach in Synthesebereichen vor der Cholesterinbildung zu liegen.

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The Effect of Ouabain on Water Consumption in the Rat

In a recent publication from this laboratory, the paradoxical 'antidiuretic' effect of chlorothiazide in animals suffering from diabetes insipidus[1,2] was interpreted as an action on the thirst centre[3]. This explanation was derived from experiments with nephrectomized rats, in which water consumption was stimulated by hypertonic salt solution, the response being suppressed by chlorothiazide.

As this group of drugs interferes with active sodium transport in the kidney[4], it appears probable that they suppress thirst by a similar mechanism, viz. by curbing active sodium transport in hypothalamic (and other) osmoreceptors[3]. If this assumption is correct, any other drug that interferes with the functioning of the sodium pump should be capable of reducing drinking and thus should exhibit an antidiuretic effect. However, KENNEDY and CRAWFORD were unable to detect such an action with organic mercurials.

The inhibitory effect of digitalis glycosides on sodium transport is well documented[5,6] and serves as a basis for their diuretic action. The latter was unequivocally established by direct injection into the renal artery[7,8]. Therefore it was anticipated that these glycosides would affect the osmoreceptors regulating water intake. This prediction was verified with ouabain (*g*-strophantin), which is much more water-soluble than other cardiac glycosides and is not bound to serum proteins[9]. Therefore a rapid action can be expected.

Method. Rats of 200–300 g body weight were bilaterally nephrectomized under ether anaesthesia. Following the operation, they were kept for 24 h with food and water supply ad libitum. They were then injected subcutaneously with 50 ml/kg of 3% NaCl and their water consumption was measured. Groups of 4 rats received intravenous injections of a given dose of ouabain in isotonic saline, while an equal volume of saline was administered to the controls.

Results and discussion. Table I reveals a marked depression of water consumption in the ouabain-treated rats during the first 2 h. The effect then fades progressively. With the lower doses of the glycoside, complete recovery is indicated by the fact that the rats reach within 24 h the same level of water intake as the controls. However, above 0.5 mg/kg, ouabain shows a long-lasting effect which extends over more than 24 h (see Table I).

If % water consumption (control = 100%) is plotted against log dose, a straight line is obtained up to 1 mg/kg (Figure). For higher doses, the curve flattens out. In evaluating these results, it should be noted that spontaneous water intake is greatly reduced by nephrectomy. Thus in the present experiments normal rats consumed 130 ml/kg/h, while the operated animals drank only 51 ml/kg in the same period. However, injection of 3% NaCl raises the water intake of nephrectomized rats as much as in intact rats and sometimes even more. Thus in 5 series of experiments, normal animals drank 55 ml/kg of water during the first 2 h after administration of hypertonic saline, while the operated rats consumed 61 ml/kg. It should be recalled here that ouabain is rapidly excreted by the kidneys, but this route is blocked in the present procedure. Therefore we have also determined the toxicity of the glycoside in nephrectomized rats (see Table II). It is evident that in the operated animals

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