PENTACYCLIC TRITERPENES AND ION EXCRETION BY THE RAT KIDNEY

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UDC 612.464:547.597

The renal excretion of water, Na^+, K^+, and creatinine was investigated in rats 3 h after administration of a 5% load of 0.9% NaCl solution by the intragastric route. The excretion of Na^+ was reduced considerably below the control level in animals receiving trihydroxylupane or heterobetulin 18-20 h before the experiment; the excretion of water, K^+, and creatinine was unchanged. After administration of dihydroxylupenal in a dose of 2 mg/100 mg body weight the excretion of Na^+ and water was increased. Heterobetulin also increased the excretion of K^+ with the urine after administration of a 5% load of 1.25% KCl solution to rats. The results are interesting from the standpoint of the study of the relationship between the structure of substances and their physiological activity.

Key words: pentacyclic triterpenes; rat kidney; ion excretion; creatinine.

Various substances from the triterpene and steroid classes are similar in structure and the biogenesis of these compounds has much in common [3, 4]. The investigation of the effect of compounds of the triterpene series on processes controlled by corticosteroid hormones is interesting. For example, certain pentacyclic acids and alcohols are known to affect the renal excretion of water and ions [1, 7]. However, it is not yet possible to say what structural elements determine their activity.

The object of this investigation was to study the effect of some pentacyclic triterpenes synthesized by the writers on certain aspects of water and mineral metabolism.

EXPERIMENTAL METHOD

Three compounds of the triterpene class were studied: dihydroxylupenal, trihydroxylupane, and heterobetulin (Fig. 1). These compounds were synthesized from the triterpene diol of betulin, present in the bark of various species of birch and therefore widely available [2, 6]. Experiments were carried out on female Wistar rats weighing 150 g. The animals were deprived of food on the day before the experiment but had free access to water.

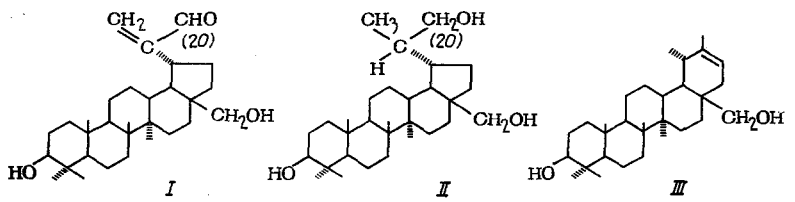

Fig. 1. Structural formulas of pentacyclic triterpenes: I) dihydroxylupenal; II) trihydroxylupane; III) heterobetulin.

Department of Chemistry of Natural Compounds, Leningrad University. Laboratory of Evolution of the Kidneys and Water and Mineral Metabolism, I. M. Sechenov Institute of Evolutionary Physiology and Biochemistry, Academy of Sciences of the USSR, Leningrad. (Presented by Academician of the Academy of Medical Sciences of the USSR S. V. Anichkov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 79, No. 3, pp. 63-65, March, 1975. Original article submitted February 27, 1974.

TABLE 1. Excretion of Na^+, K^+, and Creatinine by the Rat Kidney after Injection of Pentacyclic Triterpenes and Loading with NaCl and KCl (M±m)

Substance tested	Number of animals	Diuresis (in ml/3 h/100 g body weight	Na^+				Creatinine
			concentration in urine (in meq/liter)	excretion (in μeq/3 h	concentration in urine (in meq/liter)	excretion (in μeq/3 h	excretion (in μeq/3 h
Loading with 0.85% NaCl solution							
Control	85	2,27±0,12	155±4,5	310±15,6	41,6±2,3	75,2±3,5	399±15 (n=40)
Dihydroxylupenal	25	2,90±±0,20†	159±9,0	393±32*	35,6±2,9	75,8±6,1	466±33 (n=12)
Trihydroxylupane	23	2,31±0,18	111±7,0‡	241±21†	29,6±3,0†	58,8±6,5*	417±34 (n=11)
Heterobetulin	17	2,28±0,24	96,3±±11,6‡	169±17‡	29,2±4,6*	48,8±5,5‡	453±30
Loading with 1.25% KCl solution							
Control	12	4,80±0,38	53,1±2,8	273±32	124±8,2	485±25	464±26
Dihydroxylupenal	12	4,06±0,19	59,2±3,5	252±15	134±5,4	441±19	487±38
Heterobetulin	12	4,85±0,49	55,4±4,3	301±43	149±5,8*	616±36†	522±33

* $P<0.05$;
† $P<0.01$;
‡ $P<0.001$.

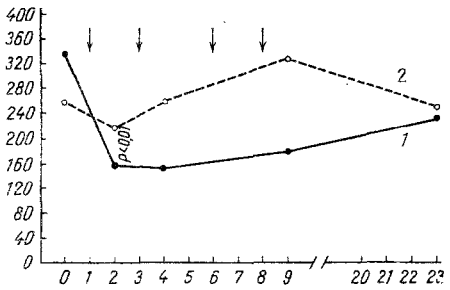

Fig. 2. Changes in Na^+ excretion during repeated injections of heterobetulin: 1) rats receiving heterobetulin; 2) control rats. Abscissa, days after first injection of preparation; ordinate, Na excretion (in μeq/3h/100 g body weight).

From 18 to 20 h before the experiment the rats received an intramuscular injection of 2 mg of the preparation in 0.5 ml oily suspension/100 g body weight. The same quantity of olive oil was injected into the control rats. Altogether 7 injections of dihydroxylupenal and heterobetulin were given over a period of 17 days and 4 injections of trihydroxylupane over a period of 8 days. The animals' renal function was tested by injecting fluid in a volume of 5% of the body weight through a gastric tube during the experiment: either 0.85% NaCl solution, 1.25% KCl solution, or distilled water was injected. The urine was collected from each rat separately in the course of 3 h. Samples of urine were analyzed for their contents of creatinine [5], Na^+, and K^+. The cations were determined on a flame photometer.

EXPERIMENTAL RESULTS AND DISCUSSION

During loading with NaCl solution, injection of dihydroxylupenal induced increased excretion of Na^+ with the rats' urine. Trihydroxylupane and heterobetulin, on the other hand, considerably reduced the Na^+ excretion (Table 1). The increase in sodium excretion induced by dihydroxylupenal was due both to an increase in the Na^+ concentration in the urine and to an increase in the volume of the diuresis. In all the series of experiments the excretion of creatinine with the urine was indistinguishable from the control, thus demonstrating the constancy of the rate of glomerular filtration. The change in Na^+ excretion after injection of all 3 compounds was thus determined by a change in the reabsorption of this ion (Table 1). These differences in the excretion of Na^+ by the experimental and control rats could no longer be detected 2 weeks after the injections of the compounds had been discontinued (Fig. 2).

Dihydroxylupenal did not affect K^+ excretion during loading with KCl solution, but after injection of heterobetulin the K^+ excretion by the kidneys was increased. The increase in K^+ excretion was accompanied by an increase in its concentration in the urine but with no appreciable change in the diuresis or the creatinine excretion. Heterobetulin administration evidently creates conditions for the more rapid excretion of an excess of K^+ from the body.

After water loading dihydroxylupenal and heterobetulin did not affect the excretion of water, Na^+, and K^+. The 3-hour diuresis in the control rats was 4.3±0.24 ml and the excretion of Na^+ was 23.4±4.5 μeq, of K^+ 50.2±8.3 μeq (n =6); after injection of dihydroxylupenal the corresponding figures were 3.7±0.16 ml and 19.1±4.0 and 47.4±6.3 μeq respectively, whereas after injection of heterobetulin they were 4.0±0.57

ml and 28.1 ± 2.0 and 44.2 ± 10.1 μeq (n=6) respectively.

In the control rats each subsequent loading with NaCl solution induced a small increase in the Na^+ excretion with the urine. In rats receiving heterobetulin, however, this was not observed. After repeated injections of the compound the Na^+ excretion remained at the level of 160 μeq/3 h/100 g (Fig. 2).

The results thus showed that the rate of excretion of Na^+ by the rat kidneys during NaCl loading is increased after injection of dihydroxylupenal but reduced after injection of trihydroxylupane and, in particular, of heterobetulin. The essential point is that dihydroxylupenal and trihydroxylupane had different actions on the excretion of Na^+ and K^+ by the kidneys, despite the fact that they have the same carbon skeleton and differ only in the groups attached at C-20. Heterobetulin, on the other hand, despite its greater differences in structure from trihydroxylupane, has a similar action to it on ion excretion by the kidney.

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