Über ein neues Analgeticum-Antipyreticum (4-Oxycumarin)

Die analgetische Wirkung des K-Vitamins[1] veranlasste uns in einer früheren Arbeit zu untersuchen, ob auch Antagonisten des K-Vitamins, also das ihm chemisch verwandte Dicumarol und seine Derivate, eine solche Wirkung haben. Diese Vermutung konnten wir bestätigen[2]. Zugleich haben wir auch sowohl auf die Verwandtschaft der Dicumarolderivate mit der Salizylsäure hinsichtlich ihrer chemischen Konstitution, als auch hinsichtlich ihres Einflusses auf den Blutgerinnungsprozess und den analgetischen Effekt hingewiesen. In einer weiteren Arbeit untersuchten wir eine Reihe neuer, dem K-Vitamin bzw. Dicumarol verwandter Verbindungen (insgesamt 19) auf ihren analgetischen, antipyretischen und sedativen Effekt. Es zeigte sich, dass 4-Oxycumarin bereits in sehr kleinen Dosen (0,025 γ/kg an der Maus und 0,1 γ/kg am Meerschweinchen) analgetisch, an der Maus auch sedativ wirkt. Am Kaninchen konnten wir auch einen antipyretischen Effekt feststellen (1 γ/kg). Die therapeutische Breite dieser Substanz ist aussergewöhnlich weit. Intramuskulär und *per os* verträgt die Maus ohne irgendwelche Störungen auch 40 mg/kg, während schon 0,025 γ/kg deutlich analgetisch wirken. Grössere Dosen verabreichten wir in Ölsuspension, weil diese Verbindung schwach wasserlöslich ist. Die bisherige allgemeine pharmakologische Analyse ergab, dass es sich um eine für das Kardiovaskularsystem sehr schwach toxische Verbindung handelt. 4-Oxycumarin erzeugt eine viel schwächere Hemmung der Blutgerinnung als Dicumarol.

4-Oxycumarin ist also das stärkste bis heute in der Literatur für Tiere beschriebene Analgeticum-Antipyreticum.

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Résumé

Le 4-oxycumarine, chimiquement voisin de l'acide salicylique, a sur les animaux de laboratoire un effet fortement analgésique, antipyrétique et sédatif.

[1] M. KUBOVIC, M. PRAŽIČ und D. ATANACKOVIČ, Proc. Soc. exp. Biol. Med. *90*, 660 (1955).

[2] P. STERN, R. KOŠAK und E. BASAGIC, Acta pharm. jugoslav. (im Druck).

Excretion and Diuretic Action of Mercurial Diuretics

WEINER, BURNETT, and RENNICK[1] recently have presented evidence of tubular secretion of the mercurial diuretic, mersalyl by the kidney of the chicken, utilizing the renal portal circulation technique of SPERBER.

Since in our laboratory we have been engaged in similar studies also using the SPERBER technique[2], the present short report of our observations supporting and extending those of WEINER *et al.* might be of some interest. The following mercurial diuretics have been investigated: Chlormerodrin NNR, [3-(chloromercuri)-2-methoxypropyl]-urea; Diurgin® (Astra, Sweden), N-succinyl-N'-[(3-carboximethylmercaptomercuri-2-methoxy)propyl]-urea disodium salt; Esidron® (CIBA, Basel), N-(3-hydroxymercuri-2-methoxy)propylamidoquinolin theophylline sodium salt; Meralluride USP, 1-(3'-hydroxymercuri-2'-methoxypropyl)-3-succinylurea theophylline sodium salt; Mercaptomerin NNR, N-[(3-carboxymethylmercaptomercuri)-2-methoxypropyl]-camphoramic acid disodium salt; Mercumatilin NNR, 8-(2'-methoxy-3'-hydroxymercuripropyl)-3-carboxycoumarin theophylline sodium salt; Mersalyl BPh, *o*-[(3-hydroxymercuri-2-methoxypropyl)carbamyl]-phenoxyacetic acid theophylline sodium salt; Oradon® (Ferrosan, Copenhagen), 3-oxymercuri-2-methoxy-1-succinimidopropyl theophylline.

(1) *Tubular excretion.*–The mercurials were infused into a leg vein and the mercury excretion from each kidney was followed. There was a marked excess of mercury excretion on the side of the infusion with most diuretics. Mercaptomerin and Diurgin® showed a highly unsymmetric excretion, mersalyl, meralluride and Esidron® showed clearly less unsymmetry. There is probably some excess excretion of chlormerodrin and no significant excess of Oradon® and mercumatilin.

(2) *Water diuresis.*–With suitable doses, a water diuresis can be obtained with all the diuretics tested. In the case of mercaptomerin, Diurgin® and meralluride, a strictly unilateral diuresis is easily obtained following injection of the mercurial into a leg vein. With carefully graded doses, it seems to be possible to obtain unilateral diuresis with all the mercurials mentioned above except Oradon® and mercumatilin. With mercaptomerin this unilateral diuresis can be achieved even if the total dose (about 1·5 mg Hg/kg) is given within 1 min. The diuresis in this case has a latency of about 15 min and a duration of about 30 min.

(3) *Salt diuresis.*– After both mercumatilin and mercaptomerin, water diuresis is accompanied by sodium and chloride diuresis with no intervening time lag. Not only the amount but also the concentration of sodium and chloride seem to increase over the basal values. The maximal increase in concentration observed with intermediate mercurial doses is 3–4 times at the height of the diuresis. Potassium excretion is not increased but rather somewhat reduced.

(4) *Prevention of unilateral water diuresis by probenecid or bromocresolgreen.*–If 20 mg/kg probenecid NNR or 10 mg/kg bromocresolgreen is injected into a pectoral muscle 30 min before the infusion of an otherwise effective dose of mercaptomerin into the leg vein, neither a bilateral nor an unilateral diuresis results. The excretion of mercury is suppressed.

(5) *Activity and biological half-life of different mercurial diuretics.*–The mercury of different diuretics leaves the body at greatly varying rates. Expressed as biological half-life of the mercury, the order of increasing biological half-life among the tested compounds is roughly: mercaptomerin, mersalyl, Esidron®, merallurid, Diurgin®, Oradon®, chlormerodrin, mercumatilin. The half-life of mercaptomerin is about 12 min, that of mercumatilin about 200 min. With mercaptomerin the amount of mercury recovered in the urine during the first 3 h is 80–100% of that administered.

The fact that the excretion properties are so very different is reflected in the varying diuretic activity. The order of increasing half-life is roughly the same as that for increasing diuretic activity per mg Hg and the same as the order of increasing length of diuretic period.

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[2] K. LINDAHL and I. SPERBER, Acta physiol. scand. *36*, 13 (1956).

These experiments will be continued and a full account published in the Acta pharmacologica et toxicologica Scandinavica.

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Résumé

Huit diurétiques mercuriels ont été étudiés selon la technique de SPERBER utilisant la circulation porte rénale de la poule. Six d'entre eux ont montrés clairement leur élimination par secrétion tubulaire. Une diurèse acqueuse peut être obtenue avec tous les diuretiques étudiés, dans la plupart des cas elle est unilatérale du côté injecté. Une diurèse Na et Cl la suit. On peut supprimer la diurèse unilatérale par la probenécide et le vert de bromocrésol. Les composés étudiés sont éliminés à des vitesses très différentes. Ceux qui présentent l'élimination la plus lente, montrent également l'activité diurétique la plus grande et de plus longue durée.

The Problem of 'Conditioning' the Action of Antiphlogistic Corticoids by the Thyroid Gland

The communications published by DOMENJOZ *et al.*[1] and STENGER *et al.*[2] report the loss of antiphlogistic activity of cortisone, ACTH and other anti-inflammatory agents after thyro-parathyroidectomy. These authors used the formalin arthritis test as indicator. SELYE could not confirm their observations. In addition to the formalin arthritis test, he also used dextran edema of the rat paw and the so-called 'granuloma pouch' as an experimental model[3]. The participation of other factors in the antiphlogistic action of corticoids seemed very interesting to us, and we tried to verify these observations using another indicator 'the cotton pellet granuloma test' modified according to MEIER *et al.*[4]. This test is frequently used in testing antiphlogistic corticoids, which decrease the quantity of newly formed granulomatous tissue around implanted cotton pellets.

Methods.—Sixty-three male Wistar rats, kept under standard conditions on Larsen diet and tap water *ad libitum*, were subdivided into 7 groups of 9 animals. The average body weight of these animals was 110–140 g. In the Group V, VI, VII thyro-parathyroidectomies were performed under ether anaesthesia. The operated animals received 100 mg/kg of calcium gluconate subcutaneously daily and 1% calcium lactate in the drinking water. After a week all animals were taken into the experiment. Cotton pellets of average weight 20 ± 1 mg were implanted subcutaneously in the interscapulary area of the back. After implantation, treatment with prednisone (1-dehydrocortisone-Ultracorten CIBA) was initiated in Groups III and VI. Each animal of these groups obtained 5 mg of prednisone *per os* daily for 7 days. In Groups IV and VII, the implanted cotton pellets were injected with a single dose of 5 mg hydrocortisone acetate on 0·2 ml of aqueous crystalline suspension (Hydrocortisate Leo). Groups I, II and V served as controls. Group I included the intact control animals, each animal of Group II received 100 mg/kg of calcium gluconate subcutaneously daily for 7 days and drank 0·1% calcium lactate to eliminate the influence of injected and ingested calcium. Finally, Group V consisted of control, thyro-parathyroidectomized animals. After 7 days, the granulomas which developed were excised in all groups and carefully dissected from the surrounding free tissue. The granulomas were dried at 54° C overnight and then weighed to estimate the dry weight. The weight of the implanted cotton pellet was then subtracted from the dry weight of the granuloma.

Results.—The principal findings are summarized in the Table. The statistical evaluation was made after FISHER[5]. The antiphlogistic corticoids given either *per os* (prednisone) or local (hydrocortisone acetate) inhibited the development of cotton pellet granuloma. Calcium gluconate alone did not influence significantly in any way the development of granuloma. Thyro-parathyroidectomized animals exhibited slightly reduced formation of granulomatous tissue. Prednisone and hydrocortisone acetate exerted a marked inhibitory effect also in thyro-parathyroidectomized animals. From these results we could not confirm the observation of DOMENJOZ and STENGER. The mechanism of antiphlogistic corticoids action is mainly direct, independent of thyroid and

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[2] E. G. STENGER, H. NAUMAN, and R. DOMENJOZ, Arch. int. Pharmacodyn. *57*, 296 (1956).

[3] P. BOIS and H. SELYE, Exper. *12*, 111 (1956).

[4] R. MEIER, W. SCHULER, and P. DESAULLES, Exper. *6*, 469 (1950).

[5] R. FISHER, *Statistical methods for research workers* (London 1934).

The effect of prednisone and hydrocortisone acetate on the formation of cotton pellet granuloma in intact and thyro-parathyroidectomized rats.

Group	Treatment	Dry weight of granuloma (mg)		
		Φ	σ	p
I	Intact control	48·3 ± 4·7	± 14·3	
II	Intact control – 100 mg/kg calcium gluconate daily	47·2 ± 3·8	± 11·4	insignificant
III	Prednisone 5 mg *per os* daily	32·8 ± 0·7	± 2·3	< 0·01
IV	Hydrocortisone acetate 5 mg local	13·9 ± 0·5	± 1·5	< 0·01
V	Thyro-parathyroidectomy control	45·0 ± 5·8	± 17·6	
VI	Thyro-parathyroidectomy – prednisone 5 mg *per os* daily	31·7 ± 0·9	± 2·6	< 0·01
VII	Thyro-parathyroidectomy – hydrocortisone acetate 5 mg local	17·0 ± 1·3	± 3·0	< 0·01

Φ statistical average; σ statistical deviation; p value of probability