

substanz für die «Hinterlappenwirkstoffe» auf, ähnlich wie das Schilddrüsenkolloid die Trägersubstanz für das Schilddrüsenhormon ist. Histochemisch scheint es sich um ein Lipoprotein zu handeln (SCHIEBLER¹).

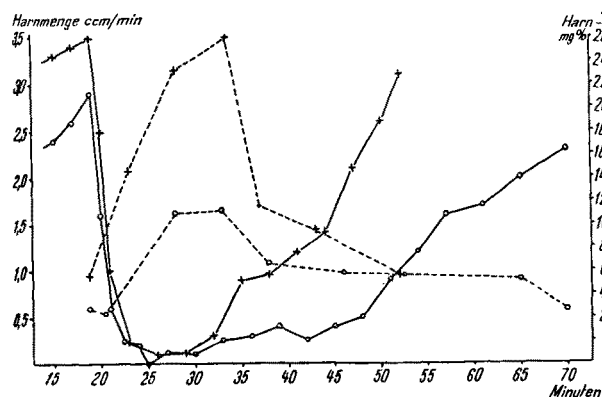


Abb. 3. Prüfung der antidiuretischen und harnkonzentrierenden Wirkung der Kernextrakte am Blasenfistelhund «Fiffi» (6,7 kg ♂). 2 Stunden vor Versuchsbeginn 100 cm³ Wasser per Schlundsonde, zum Versuch 300 cm³ Wasser. Bei einer Diurese von 2–3 cm³ Harn/min intravenöse Injektion der Extrakte in einer Dosis entsprechend dem $4,0 \cdot 10^{-5}$ -ten Teil des jeweiligen Kerns.

— + — + — Harnmenge cm³/min } *Nucleus supraopticus*
 - - - - - Chloridkonzentration mg % }
 — 0 — 0 — Harnmenge cm³/min } *Nucleus paraventricularis*
 - - - - - Chloridkonzentration mg % }

Der exakte Beweis für unsere Anschauungen bleibt einer weiteren Untersuchung vorbehalten.

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Summary

The nuclei supraopticus, paraventricularis and the tractus supraoptico-hypophyseus (tuber cinereum) of dogs were extracted by the method of the British Pharmacopoeia 1932, p. 618. These extracts have anti-diuretic, oxytoxic and pressoric activity. This suggested the idea to the authors that these hormones could have their origin in these nuclei and not in the neural lobe of the hypophysis.

¹ TH. H. SCHIEBLER, Acta Anat. (im Druck).

Preliminary Researches on the Mechanism of the Antidiuretic Action of Enteramine

It has been previously¹ demonstrated that enteramine possesses a conspicuous antidiuretic action. Subsequently the mechanism of this action and its physiological importance were investigated.

The renal clearance experiments here presented are a first contribution to the solution of these problems, which we should approach from various angles.

This study has been carried out in the dog, i.e. in the trained, colpotomized, non-anesthetized animal (blood samples were drawn from the jugular vein, urine was collected by catheterization of the bladder followed by lavage and evacuation of the organ with distilled water and insufflated air), or in the pentobarbital-anesthetized dog (catheterization of the ureters).

¹ V. ERSFAMER and A. OTTOLENGHI, Exper. 6, 428 (1950).

The glomerular filtration rate was measured by the thiosulphate clearance, the renal plasma flow by the p-aminohippuric acid (PAH) clearance $\times 1.15$, according to PHILLIPS and coworkers¹.

Both test substances were parenterally administered (750 mg/kg thiosulphate i. v., and 75 mg/kg PAH s. c.), 30–45 minutes after a water load (50 cm³/kg of light, lukewarm tea, given by gastric tube) and 45 minutes before the withdrawal of blood 1.

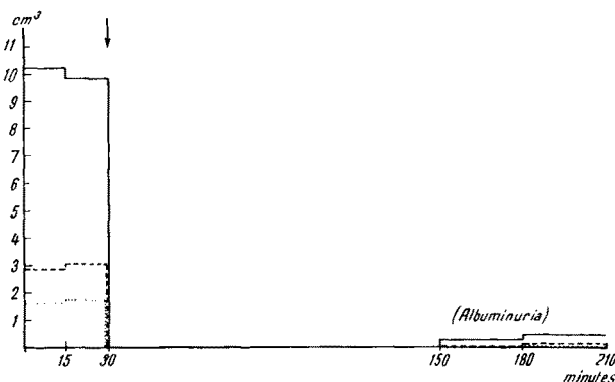


Fig. 1. – Colpotomized, non-anesthetized bitch, 14 kg. At the arrow, i. m. injection of the *Vulgaris* extract corresponding to 10 g fresh salivary tissue per kg body weight.

— renal plasma flow cm³/min/kg.
 - - - glomerular filtration cm³/min/kg.
 urine flow cm³/min/dog.

Results of two typical experiments are reproduced in figures 1 and 2. Hence, it becomes evident that the anti-diuretic action of enteramine is essentially due to a reduction or an inhibition of the glomerular filtration.

Increased tubular reabsorption, supposing it exists, could, at the best, be only of secondary importance.

The lowering of the thiosulphate clearance (the inulin clearance shows a quite similar behaviour) is accompanied by a conspicuous reduction of the tubular excretion of PAH, that is a reduction of the renal blood flow. Such, however, seems to be of minor importance and, above all, to last for a shorter time than the former.

From the preceding observations, it follows that the main cause for the reduction of the glomerular filtration must be sought in a reduced intraglomerular blood pressure, which probably is due to a spasm of the contractile structures of the afferent side of the glomerular bed (interlobar and/or afferent glomerular arteries).

It is excluded that the lowering of the intraglomerular pressure simply represents a local manifestation of a systemic hypotension. Although it is highly probable that pure enteramine itself provokes a fall of the general pressure, this is not so with crude extracts of *Octopus vulgaris* which, on the contrary, nearly always exhibit an outspoken hypertensive action (due to the presence of octopamine and tyramine).

In some of our experiments in which the carotid pressure after the i. m. or s. c. injection of large quantities of enteraminic extracts has been continuously registered, an initial pressure rise of 60–100 mm Hg was appreciable, and a subsequent slow fall to the original levels, or even somewhat below, but never lower than 100–110 mm Hg.

A constriction of the efferent side of the glomerular bed accompanying the spasm of the afferent side can at present neither be admitted nor excluded. Instead, one may

¹ R. A. PHILLIPS, V. P. DOLE, P. B. HAMILTON, K. EMERSON JR., R. M. ARCHIBALD, and D. D. VAN SLYKE, Amer. J. Physiol. 145, 314, (1946).

reasonably deny a tonus increase of the efferent artery alone, because, although such an event could easily explain the reduction of the tubular excretion of PAH, as a consequence of the diminished blood supply of the tubulus, it could by no means explain the reduction of the glomerular filtration which, on the contrary, logically should be augmented by the increase of the intraglomerular pressure.

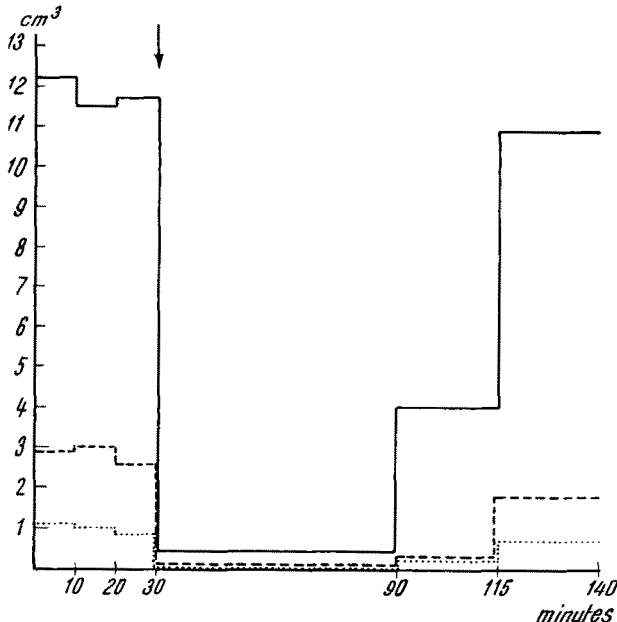


Fig. 2. – The same bitch as in figure 1, after a week. At the arrow, i. m. injection of the *Vulgaris* extract corresponding to 5 g fresh salivary tissue per kg body weight.

— renal plasma flow $\text{cm}^3/\text{min}/\text{kg}$.
 ---- glomerular filtration $\text{cm}^3/\text{min}/\text{kg}$.
 urine flow $\text{cm}^3/\text{min}/\text{dog}$.

Noteworthy indirect evidence for the inhibition of the glomerular filtration caused by enteramine may also be obtained from studying the course of thiosulphatemia in the dog. More about this will be reported in a forthcoming publication. However, it is already quite clear from our preliminary experiments that, whereas thiosulphatemia uniformly and rather quickly decreases in the control dog, in the enteramine-treated animal the decrease after the injection of a *Vulgaris* extract is suddenly interrupted, giving way, for the duration of the renal inhibition, to an almost horizontal thiosulphatemia tracing.

Four and an half hour after the i. v. administration of thiosulphate one may, for instance, still observe thiosulphatemia values of 40–50 mg per cent in those animals which were given enteramine; comparatively, thiosulphatemia values of <10 mg per cent in the control animals.

The results here obtained with massive, surely extra-physiological doses of enteraminic extracts were largely confirmed by other experiments, carried out in the rat with a dosage of enteramine 100–200 times less than above.

This investigation, a full account of which will be published elsewhere, was supported by a grant from the Italian Research Council.

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 August 14, 1950.

Zusammenfassung

Durch *Clearance*-Experimente beim Hunde konnte bewiesen werden, daß die antidiuretische Wirkung von Enteramin ausschließlich oder hauptsächlich einer Drosselung der afferenten Gefäße des Glomerulus zuzuschreiben ist.

Adrenalin- und Arterenolgehalt der Mäuse- und Rattennebenniere

Die hormonale Zusammensetzung des Nebennierenmarks weist innerhalb der Tierreihe charakteristische artspezifische Unterschiede auf. Während das Markinkret der meisten untersuchten Tierarten – *Schwein*, *Rind*¹, *Katze*, *Hund*², *Frosch*³ – und des *Menschen*² neben Adrenalin beträchtliche Mengen Arterenol (Nor-adrenalin) enthält – 20 bis 60 % –, konnten wir⁴ im Nebennierenmark von *Kaninchen* und *Meerschweinchen* nur Adrenalin nachweisen. Bei diesen beiden Tierarten ist vermutlich der für die Überführung der «Vorstufe» Arterenol in Adrenalin erforderliche *Methylierungsmechanismus* besonders wirksam. Daß andererseits das bei den meisten Tierarten im Nebennierenmark sich findende Arterenol hier nicht nur die Funktion des chemischen Intermediärproduktes zu erfüllen hat, sondern daneben auch die Funktion des selbständigen Wirkstoffs, wird dadurch wahrscheinlich, daß es unter der Einwirkung adäquater Reize (Druckentlastung des Carotissinus⁵, Splanchnicusreizung⁶) zu einer Abgabe von Arterenol aus der Inkretdrüse kommt.

Mit biologischen Differenzierungsmethoden unter Verwendung des *Katzenblutdrucks*, *Rattenuterus* und *Kaninchendarmes* als Testobjekte finden wir, daß ähnlich wie bei den meisten Tierarten auch bei der *Maus* das Nebennierenmark ein Gemisch von Adrenalin und Arterenol enthält – ungefähr 75 % Adrenalin, 25 % Arterenol –, bei der *Ratte* hingegen nur Adrenalin. Die *Ratte* würde demnach zusammen mit *Meerschweinchen* und *Kaninchen* eine Tiergruppe bilden, in deren Nebennierenmark praktisch nur Adrenalin, kein Arterenol vorhanden ist.

Wir haben wiederholt die Vermutung geäußert, daß die *pharmakologischen* Befunde vielleicht einmal eine Parallele und Bestätigung auch im «*Morphologischen*» fänden, derart, daß der histologische Nachweis zweier verschiedener Zelltypen im Nebennierenmark der Tierarten, bei denen wir beide Wirkstoffe antreffen, gelänge: eines arterenol- und eines adrenalinbildenden Typs. Das scheint jetzt der Fall zu sein, da es BÄNDER⁷ (am Pharmakologischen Institut in Marburg) ohne Kenntnis unserer Befunde offenbar gelungen ist, mit einer modifizierten Giemsa-Färbung im Nebennierenmark von *Katze*

¹ P. HOLTZ, K. CREDNER und G. KRONEBERG, Naunyn-Schmiedeberg's Arch. 204, 228 (1944–47). – P. HOLTZ und H. J. SCHÜMANN, Naturwissenschaften 35, 159, 191 (1948); Klin. Wschr. 26, 605 (1948); Naunyn-Schmiedeberg's Arch. 206, 475 (1949). – U. v. EULER, Nature 163, 642 (1949). – S. BERGSTRÖM, U. S. v. EULER und U. HAMBERG, Acta chem. scand. 3, 305 (1949). – B. F. TULLAR, Science 109, 536 (1949).

² P. HOLTZ und H. J. SCHÜMANN, Naunyn-Schmiedeberg's Arch. 210, 1 (1950).

³ H. J. SCHÜMANN, Unveröffentlichte Versuche.

⁴ P. HOLTZ und H. J. SCHÜMANN, Nature 165, 683 (1950); Arch. internat. Pharmacodyn. 83, 417 (1950). – Siehe dagegen U. S. v. EULER, Exper. 5, 451 (1949), sowie W. SCHULER und P. HEINRICH, Helv. Physiol. et Pharmacol. Acta 7, 515 (1949).

⁵ P. HOLTZ und H. J. SCHÜMANN, Naunyn-Schmiedeberg's Arch. 206, 49 (1949); 211, 1 (1950).

⁶ E. BÜLBRING und H. J. BURN, Brit. J. Pharmacol. 4, 202 (1949). – J. H. GADDUM und F. LEMBECK, Ebenda 4, 401 (1949).

⁷ A. BÄNDER, Persönliche Mitteilung.