Das Vorhandensein einer nichtlinearen Komponente in dem durch Zuwachsreize ausgelösten ERG, die offensichtlich nur unter photopischen Bedingungen demaskiert erscheint, ist für die weitere Interpretation des ERG, dessen Zustandekommen noch keineswegs als völlig geklärt betrachtet werden darf, von grossem Interesse. In laufenden Untersuchungen wird daher die Grösse und Steilheit des Zuwachsreizes und das Verhalten bei relativen Lichtlücken («decremental stimuli») näher untersucht, worüber nach Abschluss dieser Studien ausführlich berichtet werden wird. Bei dieser Gelegenheit soll auch versucht werden, die Ursachen gewisser Diskrepanzen zwischen der Arbeit von RODIECK und FORD[3] und den beim Pavian durchgeführten Untersuchungen von BRINDLEY und WESTHEIMER[2] zu finden[6].

*Summary.* Nonlinear responses may be produced by incremental stimuli in the 'global' electroretinogram of strongly light-adapted cat.

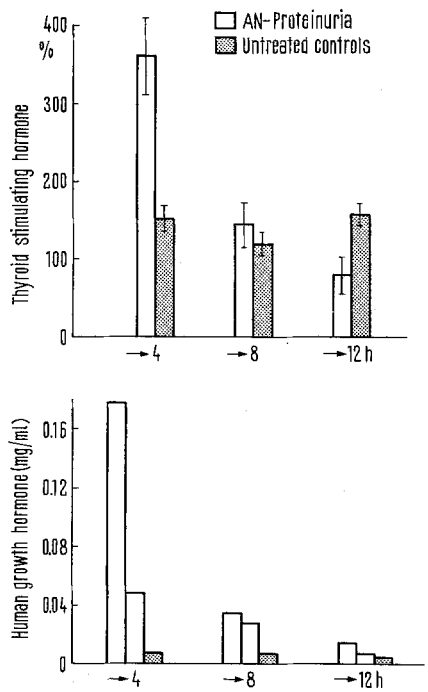
H. BORNSCHEIN, J. HOYER und A. THALER

*Institut für allgemeine und vergleichende Physiologie der Universität Wien IX (Österreich), 7. Juli 1969.*

[6] Herrn P. HEILIG sei für tatkräftige Hilfe an dieser Stelle der Dank der Verfasser abgestattet. Die benützte Datenverarbeitungsanlage wurde vom Fonds zur Förderung der wissenschaftlichen Forschung zur Verfügung gestellt.

## Passage of Pituitary Hormones Through the Nephrotic Rat Kidney and Its Possible Biological Significance

Puzzling endocrine disorders are frequently observed in a variety of diseases accompanied by hypoproteinemia. Several hypotheses have been put forward in an attempt to explain the many facets of this association, but none of them seems to be acceptable. We have recently reviewed the issue in order to provide a basis for discussing a new hypothesis[1]: it implies the loss of high molecular weight pituitary hormones along with the small hormone molecules of 'peripheral' glands in all those cases where the hypoproteinemia is caused by loss of serum proteins in the urine or into the intestinal lumen.




Above: Thyroid stimulating hormone content in the urine collected during the time period indicated on the abscissa in nephrotic (aminonucleoside-proteinuria) and untreated controls. TSH was injected i.v. at 0 time.
Below: Human growth hormone (NIH, HS 455 A) excretion in the urine of the same animals as used for the TSH assays after the i.v. injection of 1.5 mg/100 g body weight. Each white bar indicates the value obtained with the pooled urine of 2 rats.

It was decided to tackle the problem experimentally by studying the passage of the high molecular weight pituitary hormone Thyrotrophin from the blood into the urine of rats rendered nephrotic according to 2 different procedures.

In a first experiment 6 rats were injected with Aminonucleoside (Puromycin, Nutr. Bioch. Corp.) according to a procedure described by FIEGELSON[2]. With the appearance of the proteinuria (approximately 25 mg proteins/ml) the animals were given 1 U of bovine thyroid stimulating hormone (TSH) (Thytropar, Armour) per 100 g body weight. After the hormone injection the animals were kept in a plastic container specially constructed to drain the urine into an ice-cooled flask. For TSH assays the urines of all rats collected 4, 8 and 12 h after TSH injection were pooled and 8–12 aliquots were assayed from each pool.

The TSH content was measured according to McKENZIE's method[3] which takes advantage of the TSH-dose dependent secretion of radioactivity from prelabelled, thyroxine blocked mice thyroids. With this procedure the serum radioactivity before TSH injection is set as 100%. Any increase above 140% was considered to indicate the presence of significant amounts of TSH. A value of 350% corresponds in our hands to 0.5–1.0 mU TSH[4].

The results are given in the Figure. TSH is clearly demonstrable in the urine samples from nephrotic rats voided within 4 h after injection while no hormone was present at later intervals. In the urine of rats without nephrosis there was also no evidence for the presence of significant amounts of TSH. A control experiment was carried out using human growth hormone (HGH) instead of TSH (Figure, below). Although only 4 rats survived the i.v. HGH injection, the hormone excretion in the urine was certainly similar to that of TSH. HGH was measured by the hemagglutination inhibition method of GELLER and LOH[5].

[1] H. STUDER, H. W. IFF, F. WYSS and R. GUBLER, Schweiz. med. Wschr. *98*, 180 (1968).
[2] E. B. FIEGELSON, I. W. DRAKE and L. RECANT, J. Lab. clin. Med. *50*, 437 (1957).
[3] J. M. McKENZIE, Endocrinology *63*, 372 (1958).
[4] H. W. IFF, A. BURGER, H. STUDER and F. WYSS, Am. J. Physiol. *213*, 250 (1967).
[5] J. GELLER and A. LOH, J. clin. Endocrin. *23*, 1107 (1963).

The experiment was repeated and confirmed in 12 rats first injected with uranium acetate to produce proteinuria[6] and then with bovine TSH. The urine collected within 2 h after TSH injection gave a response of 387 $\pm$ 32% SEM as compared to 114 $\pm$ 5% in 6 controls. TSH was no longer detected in the nephrotic animals in any sample obtained later than 2 h after injection.

The present work confirms the hypothesis, anticipated on theoretical grounds, that exogenous polypeptide hormones of rather high molecular weight are lost from the serum into the urine of nephrotic rats. In subsequent papers we will demonstrate that the same is true for *endogenous* TSH and, moreover, that the amount of hormones lost is a biologically significant fraction of the total body pool.

*Zusammenfassung.* An Ratten mit experimentell erzeugter Proteinurie wurde gezeigt, dass das bovine thyreotrope Hormon nach i.v. Injektion von der geschädigten Niere in kurzer Zeit ausgeschieden wird. Die Versuche stützen die These, dass dem Verlust von hypophysären Hormonen in der Pathogenese von endokrinen Störungen bei Eiweissverlustsyndromen beträchtliche Bedeutung zukommt.

H. W. IFF and H. STUDER

*University Clinic of Internal Medicine, 3008 Bern (Switzerland), 14 May 1969.*

[6] A. L. SELLERS, S. ROBERTS, I. RASK and J. MARMORSTONE, J. Physiol. *183*, 406 (1955).

## H Reflex Depression by Soleus Sinusoidal Stretching and Facilitation by Voluntary Contraction

In man, stimulation of the posterior tibial nerve in the popliteal fossa produces an electromyographic response in the soleus muscle exhibiting the features of a monosynaptic reflex (HOFFMANN[1], MAGLADERY et al.[2], PAILLARD[3]). This response, termed the H reflex, generally occurs at lower intensity stimuli than those required to produce a direct motor response (M response) in the muscle. When stimuli of higher intensity are applied, the amplitude of the H reflex first increases and then diminishes along with a concomitant increase in the M response.

These changes are conveniently expressed by plotting curves relating H reflex amplitude variations to stimulus intensity (recruitment curves) (Figure 1). Such curves make it possible to detect the thresholds of the 2 responses, the maximum amplitude of the H reflex, and the ratio between reflex and motor response amplitudes. For each subject, the recruitment curves are reproducible provided that a rigorous methodology is applied (HUGON and DELWAIDE[4]).

H reflex amplitude may be greatly modified by various physiological and experimental procedures. By comparing the recruitment curves obtained under these conditions, one can estimate the intensity of the facilitatory and inhibitory influences acting on the spinal cord.

It is possible to produce a depression of the H reflex by a continuous sinusoidal movement of the ankle such that the soleus is stretched passively and periodically. Care must be taken to limit the movement to the ankle; the knee must be immobile. The conditions under which the tibial nerve is stimulated must be kept constant. This may easily be verified by observing the M response, which must remain constant during stretching even if, at the level of stimulation being studied, discrete changes in intensity can elicit marked changes in the motor response (Figure 1, T).

The effects of sinusoidal movement of the ankle were studied in 40 volunteer subjects. In each subject, significant H response inhibition occurred throughout the sinusoidal cycle. Inhibition was modulated according to the particular phase of the cycle, being more pronounced when the muscle was in a relatively stretched position. The magnitude of inhibition is a monotonic function of the amplitude and frequency of sinusoidal movement; it also varies with the initial tension of the muscle.

The figures present data obtained with a stretching frequency of 100 cycles/min and an ankle rotation of 7°. Under these conditions, no spontaneous electromyographic activity is registered in the tibial or soleus muscles. The recruitment curve obtained during sinusoidal stretching clearly exhibits a depression of the H reflex. The mechanism of this inhibition would clearly seem to implicate the proprioceptive muscle afferents, especially the Ia afferents. However, it also raises certain problems which are currently being explored.

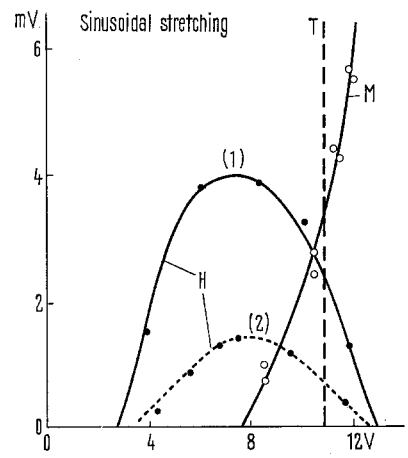



Fig. 1. This graph shows 2 recruitment curves of the H reflex. Because the values of the M responses are almost identical (see M), it is possible to compare in a given patient the curves of the H responses. The control H-curve is plotted in (1). During sinusoidal stretching, the amplitudes are depressed and the curve then obtained is drawn as (2) (datched line). T on the abscisse represents the response with an H and an M component chosen to be sure that stimulation intensity remains constant (see text).

[1] P. HOFFMANN, J. Biol. *68*, 351 (1918).
[2] J. MAGLADERY, W. PORTER, A. PARK and R. TEASDALL, Bull. Johns Hopkins Univ. *88*, 499 (1951).
[3] J. PAILLARD, Thèse Sciences, Paris Annette (1955).
[4] M. HUGON and P. J. DELWAIDE, Archs int. Physiol. *77*, 125 (1968).