J. Physiol. (1951) 112, 54–58 612.821.33:612.461.261

THE URINARY EXCRETION OF CREATININE DURING INHIBITION OF WATER DIURESIS IN MAN BY ISCHAEMIC MUSCLE PAIN

By A. R. KELSALL

From the Department of Medicine, University of Sheffield

(*Received* 23 *January* 1950)

It was shown in a previous paper (Kelsall, 1949) that water diuresis in man could be inhibited by a period of pain, induced by exercising the forearm muscles with the circulation to the arm occluded, and maintained for approximately 10 min. The inhibition so produced was of gradual onset and prolonged duration and was accompanied by marked concentration of urinary chlorides: the fall in urine volume was not related to changes in pulse rate or blood pressure, did not appear to be due to the release of any antidiuretic substance from the ischaemic muscles and could not be reproduced by the injection of adrenaline. The changes in urinary output and chloride concentration, however, closely resembled those which followed the intravenous injection of small quantities of posterior pituitary extract and it was therefore suggested that the inhibition of diuresis by pain was predominantly or wholly due to reflex stimulation of the neurohypophysis with release of the antidiuretic hormone: nevertheless, it was recognized that the experiments had not excluded the possibility that changes in glomerular filtration rate might be responsible for part or even for the whole of the fall in urine output.

It was clearly desirable to obtain further evidence on the matter. However, it was considered that the standard clearance techniques for investigating renal blood flow and glomerular filtration rate were unsuitable for the type of experiment under consideration, since additional sensory stimuli of an unpleasant nature would inevitably be introduced by the necessity for repeated venepunctures and for the injection or intravenous infusion of the appropriate chemical substances. It was therefore decided to seek further information as to the occurrence of renal vascular changes by following the urinary excretion of creatinine. Although exogenous creatinine is undoubtedly excreted partly by tubular secretion in man (Shannon, 1935; Miller & Winkler, 1938; Shannon & Ranges, 1941), endogenous creatinine appears to be excreted predominantly or wholly by glomerular filtration in persons without renal disease (Miller & Winkler, 1938; Steinitz & Türkand, 1940; Brod & Sirota, 1948); moreover, the plasma level of endogenous creatinine remains very stable during experiments

of short duration (Brod & Sirota, 1948), so that it seems justifiable to regard the urinary excretion of endogenous creatinine over limited periods as an acceptable index of creatinine clearance and thus of glomerular filtration rate. Certainly it appears unlikely that any significant fall in glomerular filtration rate could occur without a corresponding fall in the urinary output of endogenous creatinine.

METHODS

The experiments were performed as previously described (Kelsall, 1949) on four healthy males who had acted as subjects in the earlier studies. They were all medically qualified and their ages ranged from 23 to 43 years. Diuresis was induced by drinking 1 l. of tap water and the bladder was emptied by voluntary micturition at intervals of 10–30 (usually 15–20) min. Except when emptying the bladder, the subjects were seated comfortably throughout the experiments, which were begun at least 1 hr. after the previous meal: it was not considered practicable to attempt to establish 'basal' conditions or any uniform level of preliminary hydration.

Pain was induced by strong gripping movements of the right hand, the circulation to the arm being occluded by a sphygmomanometer cuff at a pressure of 180–200 mm. of mercury. The gripping movements were continued at the rate of approximately two every 3 sec. for 1½–2 min. and the severe pain so produced was maintained for a further 8–15 min., after which it was relieved by deflating the cuff.

The posterior pituitary extract used was 'Pituitrin' (Parke, Davis): solutions containing 0·05 unit/ml., adjusted to a pH of 3–4 with a potassium acetate-acetic acid buffer solution, were stored in the refrigerator in ampoules containing 1–2 ml.

Urinary creatinine was estimated by the alkaline-picrate colorimetric method described by King (1946), modified for use with an EEL photo-electric colorimeter.

TABLE 1. Effect of ischaemic pain on creatinine and water excretion during a water diuresis. Subject A.R.K. One litre tap water drunk at zero time in each experiment.

Control diuresis			Diuresis with inhibition by pain			Diuresis with inhibition by pituitrin		
Collection time (min.)	Urine vol. (ml./min.)	Creatinine excretion (mg./min.)	Collection time (min.)	Urine vol. (ml./min.)	Creatinine excretion (mg./min.)	Collection time (min.)	Urine vol. (ml./min.)	Creatinine excretion (mg./min.)
30	0·8	1·24	20	1·5	1·08	20	1·9	1·15
60	5·4	1·19	40	5·6	1·01	40	5·5	1·04
80	9·0	1·22	50	9·9	0·97	51	7·6	0·92
100	9·3	1·21	64*	11·9	0·97	61†	9·9	0·99
120	6·8	1·16	74	4·4	0·86	71	1·2	1·03
140	3·9	0·94	85	2·2	0·85	83	0·9	1·03
160	1·9	1·00	97	2·3	0·81	95	1·2	1·17
180	1·3	1·03	111	4·6	0·88	115	1·5	0·99
—	—	—	129	7·7	0·84	135	4·0	0·92
—	—	—	145	7·5	0·79	155	7·5	0·97
—	—	—	166	5·9	0·74	175	7·1	0·89
—	—	—	186	3·1	0·72	195	3·8	0·79
—	—	—	206	2·0	0·8	215	2·0	0·84

* Pain for 8 min. during this period.
† Pituitrin 0·05 unit intravenously during this period.

RESULTS

The creatinine excretion was followed in each subject during a control period of water diuresis, during water diuresis with inhibition by pain and during water diuresis with inhibition by the intravenous injection of 0·05–0·1 unit of

posterior pituitary extract. Each experiment was performed once on three subjects and three times on subject A.R.K. The detailed results of one experiment, typical of all six performed, are given in Table 1 and the results of another are illustrated in Fig. 1. During control water diuresis in subject A.R.K. there was a tendency for creatinine excretion to diminish throughout the experiment:

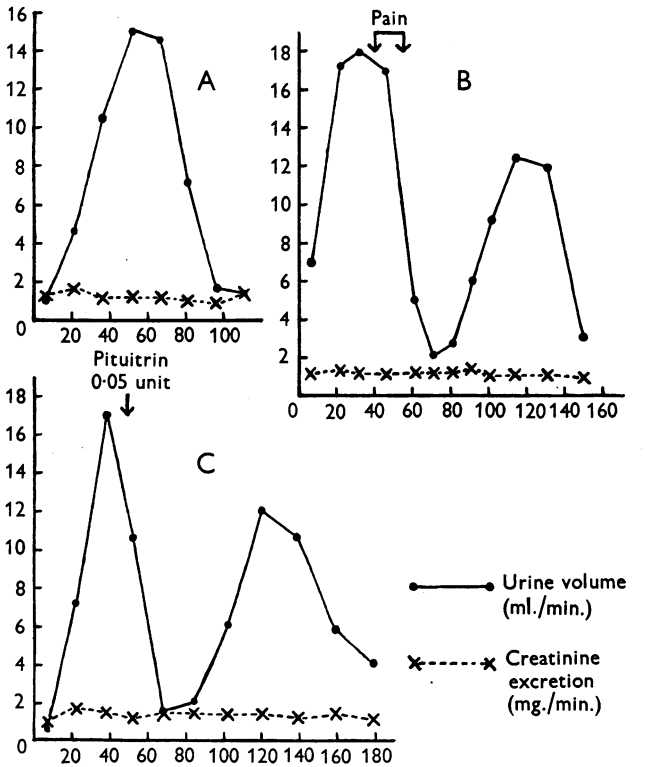

Fig. 1. Subject D.A.T. Urinary creatinine excretion during control diuresis, during diuresis with inhibition by pain and during diuresis with inhibition by intravenous posterior pituitary extract. Ordinates: urine volume in ml./min., urine creatinine excretion in mg./min., both charted at midpoint of corresponding period of collection. Abscissae: time in min. One litre of tap water drunk at zero time in each experiment. A, control diuresis. B, effect of pain for 15 min. C, effect of 0·05 unit posterior pituitary extract intravenously.

this may perhaps have been due to gradual approximation of the subject to 'basal' conditions. The changes in creatinine output, however, were very small compared with the changes in urinary volume, with which they showed no correlation. A similar slight downward trend in creatinine excretion was observed over a corresponding 3 hr. period in subject A.R.K. when diuresis was not induced. In the other three subjects, creatinine excretion showed no tendency to fall during water diuresis.

In the experiments in which diuresis was inhibited by pain, there was no significant change in creatinine excretion during the three periods immediately following pain, when inhibition of urine flow was maximal, compared with previous and subsequent periods (*t* test). Similarly, the excretion of creatinine did not show any significant change during the three periods following the injection of posterior pituitary extract, though the variability was somewhat greater than after pain.

DISCUSSION

The absence of any change in creatinine excretion parallel with, or comparable to, the changes in urinary volume during water diuresis or during inhibition of diuresis by posterior pituitary extract is in conformity with previous work. No significant change in glomerular filtration, measured by the inulin clearance, was found during water diuresis in man by Chasis, Ranges, Goldring & Smith (1938), and no change in glomerular filtration rate, measured by xylose or sucrose clearances, was found during 'pitressin' anti-diuresis in man by Burgess, Harvey & Marshall (1933).

In the six experiments in which diuresis was inhibited by pain, the results were consistent. If it is conceded that any significant fall in glomerular filtration rate would be accompanied by a corresponding drop in the urinary excretion of creatinine, it is clear that there is no large, constant or sustained decrease in glomerular filtration rate during inhibition of water diuresis in man by ischaemic muscle pain, nor any change comparable with the diminution in urine volume. These findings were not unexpected. Although a marked decrease in renal blood flow can be produced in man by pain (Wolf, 1943) or by alarm (Smith, 1939–40), the glomerular filtration rate may, nevertheless, remain essentially unchanged (e.g. Smith, 1939–40, fig. 7; Wolf, 1943, table 18, exp. 5); in fact, the glomerular filtration rate always tends to remain relatively stable in spite of very wide variations in renal blood flow, probably because renal vasoconstriction occurs predominantly at the efferent glomerular arterioles (Smith, 1939–40). It is considered therefore that the experiments here reported lend further support to the hypothesis that the inhibition of diuresis produced in man by ischaemic muscle pain is largely or entirely due to reflex stimulation of the neurohypophysis with release of the antidiuretic hormone.

SUMMARY

1. The urinary excretion of endogenous creatinine remained substantially unchanged in four normal male subjects during inhibition of water diuresis by ischaemic muscle pain and during inhibition by the injection of posterior pituitary extract.

2. Reasons are given for the view that these findings support the hypothesis that the inhibition of diuresis produced by pain is predominantly or wholly due to release of antidiuretic hormone from the neurohypophysis.

I wish to express my thanks to my colleagues L.K., R.E.H.P. and D.A.T. for participating in these experiments; to Dr A. Jordan for statistical analysis of the experimental results; to Mr W. Forshall and Dr M. W. A. Gatman for advice on the estimation of creatinine; to Mr A. F. Nicholls for performing the initial calibration of the colorimeter and for other technical assistance; and to Miss K. M. Radcliffe for preparing the dilute solutions of 'pituitrin'.

REFERENCES

Brod, J. & Sirota, J. H. (1948). *J. clin. Invest.* **27**, 645.
Burgess, W. W., Harvey, A. M. & Marshall, E. K. Jr. (1933). *J. Pharmacol.* **49**, 237.
Chasis, H., Ranges, H. A., Goldring, W. & Smith, H. W. (1938). *J. clin. Invest.* **17**, 683.
Kelsall, A. R. (1949). *J. Physiol.* **109**, 150.
King, E. J. (1946). *Micro-Analysis in Medical Biochemistry.* London: J. and A. Churchill Ltd.
Miller, B. F. & Winkler, A. W. (1938). *J. clin. Invest.* **17**, 31.
Shannon, J. A. (1935). *J. clin. Invest.* **14**, 403.
Shannon, J. A. & Ranges, H. A. (1941). *J. clin. Invest.* **20**, 169.
Smith, H. W. (1939–40). *Harvey Lect.* **35**, 166. Lancaster, Pennsylvania: The Science Press Printing Company.
Steinitz, K. & Türkand, H. (1940). *J. clin. Invest.* **19**, 285.
Wolf, G. A. (1943). *Res. Publ. Ass. nerv. ment. Dis.* **23**, 358.