Extrarenal Effects of Intravenous Pitressin in Nephrectomized Rats

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Using inulin as indicator of the extracellular fluid volume, the effects of Pitressin on the movements of sodium and potassium were studied in the nephrectomized rat together with simultaneously determined direct blood pressure values. Pitressin caused a movement of sodium and water into cells coupled with the extrusion of some potassium during the phase of blood pressure elevation. The beginning of the phase of blood pressure decline coincided with a rapid shift of potassium into cells while the sodium and water acquired by cells in the early phase were gradually extruded. These shifts were demonstrable with as little as 10 mU. of Pitressin intravenously while the maximal effect occurred in the 30 to 50 mU. dose range. These effects may account for many of the changes observed with Pitressin in the intact animal and also may have some bearing on blood pressure homeostasis.

IN THE mammal, the antidiuretic hormone is usually considered to exert its effect exclusively on the kidney. It has been difficult, however, to rationalize this view with all the conflicting data concerning the effect of Pitressin in this class and, indeed, to harmonize it with observations in other classes of vertebrates. The problem has apparently not been subjected to direct experimentation in several decades, although indirect studies have several times suggested the possibility of an extrarenal site of action.

Recent studies related to the problem of hypertension have led us to define new actions for Pitressin. The present report deals with the extrarenal effects of Pitressin administered intravenously.

The method of approach was based on a study of the dynamic flux of extracellular sodium, potassium, and water in recently nephrectomized rats. The procedure ordinarily used for the in vitro study of tissues with inulin as extracellular space indicator was extended as an in vivo method. The primary concern throughout was not with the absolute amount of a given constituent in the extracellular space at a static period but rather with its change during various time intervals following Pitressin injection. These studies indicate basic extrarenal actions for this extract. They also provide basic information concerning mechanisms underlying blood pressure elevation.

METHODS

Male albino rats of an inbred Wistar strain, weighing 180 to 250 Gm., were used throughout. Each experiment was carried out in sections, with 2 groups of at least 8 rats each; one to serve as control, the other to receive Pitressin. Both groups were bilaterally nephrectomized, allowed a one-hour recovery period, and then injected with inulin, 3 mg. in 0.15 ml. saline/100 Gm. directly into the right femoral vein. Two hours without further handling were then allowed as an equilibration period for the inulin. At the end of this period, a zero time direct blood pressure determination followed immediately by the collection of 0.6 ml. of blood was carried out using the left femoral artery. The appropriate dose of Pitressin in 0.1 ml. of saline was at once injected into the left femoral vein in the test rats, the saline alone in the controls. Blood pressure was recorded from the femoral artery through a 22 gage needle coupled with a Sanborn

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This work was carried out with the aid of a grant from the Ciba Company, Limited.

Received for publication March 20, 1966.

The Pitressin powder used in this work was supplied through the courtesy of Dr. D. A. McGinty of Parke, Davis and Company.
### Table 1.—The Distribution of Na, K, Water, and Blood Pressure Following the Intravenous Injection of 0.5 I.U. of Pitressin

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<tr>
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Effects are tabulated in terms of change from the initial value during the particular interval. C = control; T = test.  
* = p < 0.01 or < 0.02.
blood pressure cannula. Sodium and potassium were determined using a Beckman model B flame photometer. Pitressin was made up fresh from standardized powder dissolved in saline as required. All operative procedures were carried out using light ether anesthesia (the same results were obtainable with Nembutal as anesthetic).

Calculations were carried out for each rat separately. Extracellular fluid volume (e.c.f.v.) was calculated from the inulin concentration as the volume distribution of the injected inulin. Extracellular sodium and potassium (e.c.Na, and e.c.K) were calculated as the product of e.c.f.v. and Na or K concentration as determined in plasma. Since the absolute value for e.c.f.v., e.c.Na, and e.c.K depended on the accuracy of the inulin injection, this variable was reduced by expressing all values other than blood pressure as percentage change from the initial or zero time datum. This has the further advantage of expressing all determinations on a percentage yardstick which facilitate plotting of shifts on the same scale. For blood pressure, the change during the interval was expressed simply as change in mm. Hg. The data for individual animals of each group were then averaged and compared statistically as required. Accordingly, the emphasis of this study is on the degree and direction of change.

RESULTS

The Effects of a Large Dose of Pitressin. Experiment 1 was designed to study the effect of a large dose of Pitressin on the distribution of water, sodium, and potassium, together with the simultaneous effects on the blood pressure. The test dose was 0.5 I.U. administered in 0.1 ml. of saline. The experiment required 7 separate sections with 8 control and 8 test animals in each. Each section dealt with one time interval after Pitressin injection. The intervals studied were 5, 10, 20, 30, 40, 50, and 60 min. in length. The detailed procedure was exactly as described. The essential results are presented in table 1 and, in part, in figure 1.

The first effect of Pitressin was to induce a movement of sodium and an apparently isosmotic volume of water into the cellular compartment. The subsequent return to normal was a slow process complete only 40 min. after injection with a suggestion of a subsequent rebound phenomenon. Since the methods used were relatively crude and yet significant results were obtained at individual points, the shift in sodium and water must have been sizeable and consistent. It is not possible to be dogmatic about the relative amounts of sodium and water involved. Inspection of the table shows that although the concentration of sodium in plasma did not change significantly at any 1 period, it was consistently reduced in the test group during the first 5 periods. This suggests that relatively more sodium than water was involved in the transfer into the cellular compartment.

The second effect of Pitressin was on the entry of potassium into the cellular phase and this occurred at the time the blood pressure began to fall. The fact that this change occurred later in time than the initial entry of sodium and water into cells accounts, in this experiment, for the fact that potassium concentration as measured in plasma was sharply elevated during the first 2 periods. The rebound to this was noted as a sharp reduction in potassium concentration at the 40 min. period.

The Dose-Response Curve. Six separate sections were used for experiment 2. The results for 0.5 I.U. were available from the previous experiment. The response in the 5 min. inter...
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Effects are tabulated as change from the initial value during the 0-5 min. interval. C = control; T = test.
* = p < 0.01 or <0.02.
† = Suggestive change.
val was used to measure the effects of graded doses. For most dose levels, 8 control and 8 test animals were sufficient. Larger groups were necessary for the lower and more critical 10 and 5 mU. dose levels. The detailed procedure was as described. The results are presented in table 2 and, in part, in figure 2.

The movement of sodium and water into the cellular phase was a regular response and followed a hyperbolic curve related to dose. Significance at individual points was obtained as far down as the 10 mU. level and it is probable that a larger series and small increase in accuracy would extend this down to 1 mU. The peak response occurred between 30 and 50 mU. The blood pressure curve was entirely similar with its origin and peak similarly placed with respect to dose. Changes in potassium concentration in this 5 min. interval were apparently secondary to movements of water.

The Effects of a Low Dose of Pitressin. The effects of 30 mU. of Pitressin on sodium, potassium, water and blood pressure were studied at various intervals after injection in experiment 3. Five separate sections were used to study the intervals of 2, 5, 10, 20 and 30 min. The detailed procedure was as described. The results are presented in table 3.

The curves obtained were basically similar to those of experiment 1, differing mainly in the lesser intensity and duration of effect. Again, sodium and water moved into cells while blood pressure rose steeply. They were slowly extruded again as the pressure returned to normal. The addition of the 2 min. interval to this study showed up a trend for extracellular potassium to increase in amount coincident with the pressure rise and beginning entry of sodium into the cells.

DISCUSSION

The findings amplify our previous observations with subcutaneous Pitressin\(^4\) and leave little doubt about the extrarenal effects of the extract or their magnitude in the rat. Since 10 mU. moves approximately 6 per cent of the extracellular fluid, or about 1.2 ml. in a 200 Gm. rat, into the cellular compartment, simple extrapolation shows that this effect can easily underlie the antidiuretic effect of even much smaller doses. It seems unnecessary to assume that a different process supervenes at very low doses.

These results cannot be a false effect due to some inherent error in the inulin technic. The decrease in e.c.f.v. represents an increase in inulin concentration. Were this in error, the sodium, potassium and water curves would all tend to parallel one another, whereas, clearly, the various effects can be readily separated out.

We cannot solve in any positive way the problem of whether, in addition to the extrarenal effects, Pitressin has any special renal action. Starling and Verney\(^8\) demonstrated an apparent direct renal effect 30 years ago and the position has not been seriously challenged since. At the present time, we are not persuaded that the renal effect of Pitressin is a special function; it may well be the expression of a general function in a special tissue.

The movement of sodium into cells under the influence of Pitressin suggests that a simple explanation for Pitressin-induced chloruresis

![Fig. 2. Log dose of intravenous Pitressin plotted against the change in extracellular sodium, water and systolic blood pressure during the 0-5 min. interval after injection. Graphs prepared from data of table 2 by expressing the simultaneously determined control value in each case as a zero baseline. ◦ = systolic blood pressure; ◯ = extracellular sodium; ○ = extracellular water.](http://circres.ahajournals.org/)
Diastolic B.P., change, mm.
Hg
C  
T  
Diastolic B.P., change, mm.
Hg
C  
T  
Mean B.P., change, mm. Hg
C  
T  
e.c.f.v., % change
C  
T  
ee.c. K, % change
C  
T  
ee.c. Na, % change
C  
T  
Plasma Na, % change
C  
T  
Plasma K, % change
C  
T  
e.e. Na, % change
C  
T  
e.e. K, % change
C  
T  
Average body wt., Gm.
C  
T  
No. of animals
C  
T
Effects are tabulated in terms of change from the initial value during the particular interval.  C = Control;  T = Test.
* =  p < 0.01 or < 0.02.
† = suggestive change.
‡ = unusual and probably misleading value.

might be the concomitant excretion of extra negative, unbound charges. The slow later extrusion of the newly acquired intracellular sodium tallies with the findings of Conway and Hingerty16 as do the more rapid shifts of potassium into and out of the cells. It also seems quite possible that one basic process may explain the antidiuretic-chloruretic effect of low doses of Pitressin and the diuretic-natriuretic effect of high doses. Certainly, these findings and their theoretical extensions fit much better with our other observations concerning Pitressin.5,6 Indeed, these latter findings suggested the need for a re-examination of our basic ideas about Pitressin.

A second and equally important area involved in these experiments concerns the relation of sodium to blood pressure, and these studies were designed to add information on this subject. They would seem to have done so. The association between the movement of sodium (and water) and the blood pressure is well beyond the realm of chance. They correlate not only in degree but in dose-response as well. Since this is a larger problem, evidence will be reported separately to demonstrate...
that this sodium-water shift is a general physiologic phenomenon causally implicated as a
basic mechanism in vascular smooth muscle
contraction and the elevation of blood pres-
sure. The mechanisms which provide for the
transfer of sodium into and out of cells, that
is, the “sodium pump mechanisms” broadly
defined, are affected not only by Pitressin, as
seen here, but by adrenaline, noradrenaline
and histamine as well as in experimental hyper-
tension. Recent studies by Tobian and Fox11
are in agreement with this general theory as
stated here. It seems likely that these findings
bear on the basic defect in essential hyperten-
sion.

SUMMARY

The effects of Pitressin on blood pressure
and on the movement of water, sodium, and
potassium were followed in the nephrecto-
mized rat. One hour after bilateral nephrec-
tomy a known amount of inulin was injected
into the right femoral vein and 2 hours allowed
for equilibration. Following this, zero-time
blood pressure was measured and 0.6 ml. of
blood collected from the left femoral artery.
Pitressin in 0.1 ml. of saline was at once in-
jected into the left femoral vein in the test
rats, saline alone in the controls. A second
blood pressure and blood sample was obtained
from the same left femoral artery after an ap-
propriate interval. The effect of 0.5 I.U. of
Pitressin was followed through 7 intervals
from 5 to 60 min. after injection. A dose-re-
sponse curve was then constructed using 7
doses to cover the range of 500 mU. down to
1 mU. Finally, the effects of a small dose, 30
mU., were followed through five intervals from
2 to 30 min. after injection.
Pitressin caused sodium and water to move
into cells. The degree of this shift correlated
with the rise in blood pressure. During this
phase, plasma potassium rose, partly because
of the movement of water and partly because
of an outward displacement of cellular potas-
sium. The later decline in blood pressure tended
to coincide with the beginning of potassium
re-entry into cells. The sodium and water
which initially entered the cells was gradually
extruded. These changes were detectable with
significant individual points down to the 10
mU. dose level. In addition to elucidating
the basic mechanisms of Pitressin action, these
data bear directly on the nature of the basic
mechanisms in blood pressure homeostasis.

SUMMARIO IN INTERLINGUA

Esseva studiate le effectos de Pitressina super
le pression sanguinee e super le movimento de
aqua, natrium, e kalium in nephrectomisate
rattos. Un hora post nephrectomia bilatere un
quantitate cognoscite de inulina esseva injicite
in le dextere vena femoral. Un intervallo de duo
horas esseva permittite pro effectuar le equili-
bration. Postea le pression sanguinee neutre
(a tempore zero) esseva mesurate, e 0,6 ml. de
sanguine esseva colligite ab le sinistre arte-
ria femoral. Pitressina in 0,1 ml. de solution salin
esseva immediatemente injicite in le sinistre
vena femoral del rattos de proba; solution
salin sin Pitressina esseva injicite in le rattos
de controlo. Un secunde mesuration del pres-
sion sanguinee e un secunde specimen de san-
guine esseva obtenite ab le mesme sinistre
arteria femoral post le passage de un appro-
priate intervallo de tempore. Le effecto de 500
milliunitates international de Pitressina esseva
traciate in un serie de septe intervallos de ab
5 a 60 min post le injection. Postea un curva
del reaction como function de dosage esseva
construite ex observationes con septe doses
representante le scala ab 500 a 1 milliunitates.
Finalmente, le effectos de un parve dose de 30
milliunitates esseva traciate in un serie de
cinque intervallos de ab 2 a 30 min post le
injection.
Pitressina effectuava un transferimento de
natrium e aqua a intra le cellulas. Le grado de
iste transferimento se monstrava in correlation
con le augmento del pression sanguinee. Du-
rante iste phase, le kalium del plasma se aug-
mentava, in parte a causa del movimento de
aqua e in parte a causa del transferimento
eextrorse del kalium cellular. Le subsequente
decline del pression sanguinee coincideva plus
o minus con le comenciamento del re-entrata
de kalium a in le cellulas. Occurreva un extrusion
gradual del natrium e aqua que initialmente
EXTRARENAL EFFECTS OF PITRESSIN IN NEPHRECTOMIZED RATS

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HABEVA PENEITRATE LE CELLULAS. ISTE ALTERATIONES ESSEVA DETEGIBLE (CON SIGNIFICATIVE PUNTOS INDIVIDUAL) AB LE PLUS ALTE USQUE AL NIVELLOS CORRESPONDENTE A UN DOSE DE 10 MILLIUNITATES. ISTE OBSERVATIONES CONTRIBUE AL CLARIFICATION DEL MECHANISMOS FUNDAMENTAL DEL ACTION DE PITRESSINA, SED ILLOS ETIAM PROMOVE NOSTRE CONNOBENTIAS IN RE LE NATURA DEL MECHANISMOS FUNDAMENTAL QUE DETERMINA LE HOMEOSTASE DEL PRESSION SANGUINEE.

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Circ Res. 1956;4:557-564
doi: 10.1161/01.RES.4.5.557

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