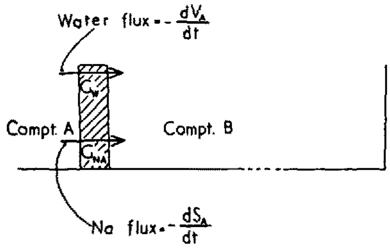
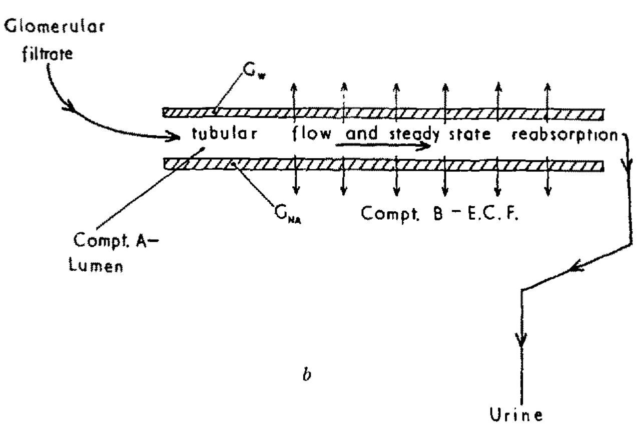
A Theoretical Consideration of the Interaction of Antidiuretic Hormones and Sodium Retaining Hormones in the Kidney

The transfer of Na and water across frog skin has been studied in some detail and it seemed possible that the renal tubular processes might be not entirely dissimilar A model 'renal tubule' is proposed in which the permeability of the tubule wall to water would be increased in the presence of anti-diuretic hormone (A.D.H.) and in which sodium reabsorption would be an active process, as envisaged by USSING and ZERAHN[1], controlled by a sodium retaining hormone (S.R.H., possibly a mineralocorticoid). We do not propose to discuss the morphology of the renal tubule or of its reabsorptive processes. We will assume that the factors characterizing the reabsorption of water and sodium are constant over the whole length of the tubule. In this case it may be shown that the above system is analogous to a tank of saline divided into two compartments A and B by a membrane permeable to both sodium and water in one direction and impermeable to both in the opposite direction. The permeability of the membrane to water is considered to be controlled by A.D.H., and the transfer of Na to depend upon the activity of a sodium pump (controlled by S.R.H.) acting across the membrane.



a

Fig. 1 *a*.—Representing Na and water fluxes between two compartments, A and B, separated by a membrane whose permeabilities to Na and water are G_{Na} and G_w respectively. S_A is the quantity of sodium in A; V_A the volume of water in A.



b

Fig. 1 *b*.—Representing a simplified model of a renal tubule whose reabsorptive properties are uniform over the whole of its length.

In the absence of forces across the membrane other than those due to difference in sodium concentration between compartments A and B we have:

Force tending to transfer Na from A to B

$$= K\left\{ \mathrm{Ln}\,\frac{S_A(t)}{V_A(t)} - \mathrm{Ln}\,\frac{S_B(t)}{V_B(t)} \right\}$$

and force tending to transfer water from A to B

$$= K\left\{ \mathrm{Ln}\,\frac{S_B(t)}{V_B(t)} - \mathrm{Ln}\,\frac{S_A(t)}{V_A(t)} \right\}.$$

Thus the fluxes of sodium and water i_{Na} and i_w respectively, are given by:

$$i_{Na} = \begin{cases} K\left\{ \mathrm{Ln}\,\frac{S_A(t)}{V_A(t)} - \mathrm{Ln}\,\frac{S_B}{V_B} \right\} G_{Na} & \text{if } \frac{S_A}{V_A} > \frac{S_B}{V_B}\,; \\ 0 \quad \text{if } \frac{S_A}{V_A} \leqslant \frac{S_B}{V_B}\,. \end{cases} \qquad (1)$$

$$i_w = \begin{cases} K\left\{ \mathrm{Ln}\,\frac{S_B}{V_B} - \mathrm{Ln}\,\frac{S_A(t)}{V_A(t)} \right\} G_w & \text{if } \frac{S_B}{V_B} > \frac{S_A}{V_A}\,, \\ 0 \quad \text{if } \frac{S_B}{V_B} \leqslant \frac{S_A}{V_A}\,. \end{cases} \qquad (2)$$

The system tends to an equilibrium condition in which

$$\left(\frac{S_A}{V_A} = \frac{S_B}{V_B} \right)$$

whatever the initial concentration in A.

In the presence of E_{Na} and P the equations (1) and (2) defining sodium flux and water flux become:

$$i_{Na} = \begin{cases} \left[E_{Na} + K\left\{ \mathrm{Ln}\,\frac{S_A(t)}{V_A(t)} - \mathrm{Ln}\,\frac{S_B}{V_B} \right\} \right] G_{Na} \\ \qquad \text{if } \left[E_{Na} + K\left\{ \mathrm{Ln}\,\frac{S_A(t)}{V_A(t)} - \mathrm{Ln}\,\frac{S_B}{V_B} \right\} \right] > 0\,; \\ 0 \quad \text{if } E_{Na} + K\left\{ \mathrm{Ln}\,\frac{S_A(t)}{V_A(t)} - \mathrm{Ln}\,\frac{S_B}{V_B} \right\} \leqslant 0\,; \end{cases} \qquad (3)$$

$$i_w = \begin{cases} \left[P - K\left\{ \mathrm{Ln}\,\frac{S_A(t)}{V_A(t)} - \mathrm{Ln}\,\frac{S_B}{V_B} \right\} \right] G_w \\ \qquad \text{if } \left[P - K\left\{ \mathrm{Ln}\,\frac{S_A(t)}{V_A(t)} - \mathrm{Ln}\,\frac{S_B}{V_B} \right\} \right] > 0\,; \\ 0 \quad \text{if } \left[P - K\left\{ \mathrm{Ln}\,\frac{S_A(t)}{V_A(t)} - \mathrm{Ln}\,\frac{S_B}{V_B} \right\} \right] \leqslant 0 \end{cases} \qquad (4)$$

respectively.

Table I.

$V_A(t)$	Volume of water in compartment A at time t.
$V_B(t)$	Volume of water in compartment B at time t.
$S_A(t)$	Quantity of sodium in compartment A at time t.
$S_B(t)$	Quantity of sodium in compartment B at time t.
G_{Na}	Membrane permeability to sodium in direction $A \rightarrow B$ assumed independent of flux.
G_w	Membrane permeability to water in direction $A \rightarrow B$ assumed independent of flux.
i_{Na}	Sodium flux in direction $A \rightarrow B$.
i_w	Water flux in direction $A \rightarrow B$.
E_{Na}	Electromotive force developed by the membrane sodium pump in direction A to B.
P	Force favouring water transfer in direction A to B (e.g. hydrostatic pressure difference).

Further let $V_B \gg V_A$ so that the error in taking $V_A + V_B = V_B$ may be neglected.

[1] H. H. USSING and K. ZERAHN, Acta physiol. scand. *23*, 110 (1956).

Table II. Values of constants and parameters.

α	S_A/V_A in the steady state.
G_w	is a parameter: with a NaCl ratio of 1:10 across frog-skin, the water flux is about 10 μl/cm²/h. (KOEFOED-JOHNSON and USSING, 1953; CAPRARO and GARAMPI, 1956). From these figures, G_w may be expressed as a membrane conductivity of $4{\cdot}6 \times 10^{-8}$ ml/s/cm²/mV.
	In presence of A. D. H. G_w may be more than doubled.
E_{Na}	is a parameter: USSING and ZERAHN (1951) give values of about 70 mV for frog-skin.
K	is a constant and $= RT/nF$ where $n = 1$ and is taken as 26·6 mV.
G_{Na}	is the same as k_{Na} used by USSING and ZERAHN (1951) and is equal to $6{\cdot}2 \times 10^{-9}$ mEq/s/cm²/mV.
P	is a parameter of the system given, for convenience, in millivolts.

It may be shown that if either or both P and $E_{\text{Na}} > 0$ no equilibrium condition exists but that a steady state exists in which i_w and i_{Na} take *non-zero* values such that

$$\frac{S_A(t)}{V_A(t)}$$

remains constant. In this case it may be shown that

$$\frac{i_{\text{Na}}}{i_w} = \frac{S_A}{V_A} = \alpha, \tag{5}$$

where α is a constant.

Hence eliminating i_{Na} and i_w between equations (3), (4) and (5) we have

$$Ln\,\frac{S_A(t)}{V_A(t)} = Ln\,\frac{S_B}{V_B} + \frac{\alpha\,P\,G_w - E_{\text{Na}}\,G_{\text{Na}}}{K\{G_{\text{Na}} + \alpha G_w\}} \tag{6}$$

which defines the steady state.

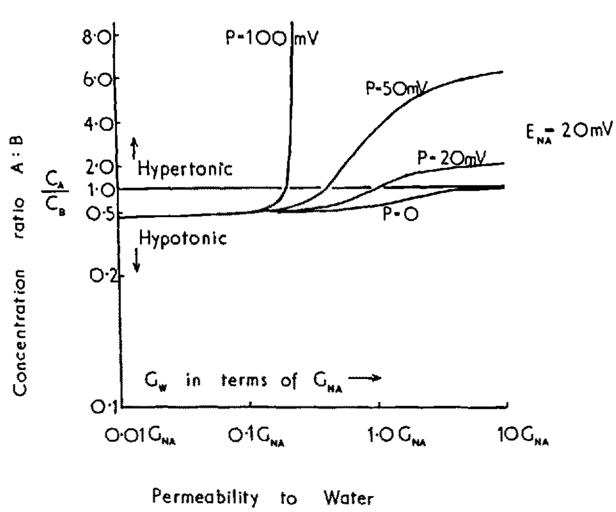


Fig. 2*a*.—The effect of P upon the steady-state concentration ratio between A and B (C_A/C_B), plotted as a function of G_w with E_{Na} = 20 mV.

It may be seen from the Figures 2*a* and 2*b*, which are graphs of

$$\frac{S_A/V_A}{S_B/V_B}$$

plotted as a function of G_w with E_{Na} and P as parameters, that the concentration ratio across the membrane

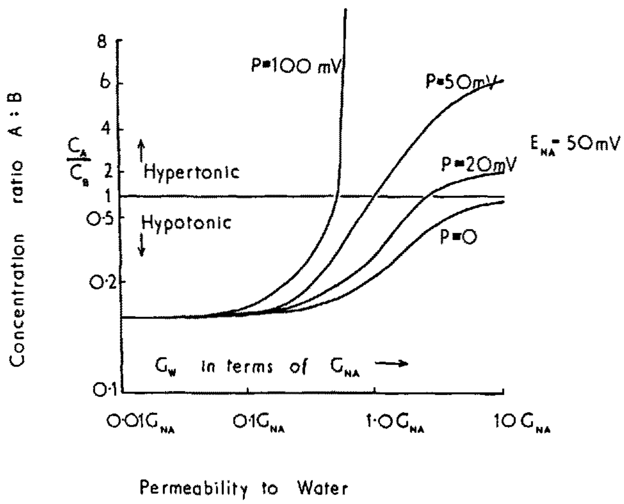


Fig. 2*b*.—The effect of P upon the steady-state concentration ratio between A and B (C_A/C_B), plotted as a function of G_w with E_{Na} = 50 mV. For details of parameters in these figures, see text.

in the steady state is, for any given P, a function of both E_{Na} and G_w. This is the phenomenon of interaction.

A thorough examination of equation (6) reveals facts which may be shown to correspond to certain physiological findings as discussed below:

(1) If sodium reabsorption (E_{Na}) be reduced, the equation reveals that the condition favours increased water excretion. This is evident in the case of mercurial diuretics[2].

(2) When water reabsorption is reduced (e.g. G_w is reduced due to fall of A.D.H. level) sodium excretion may be increased, as is found in water diuresis or hypotonic saline diuresis[3].

(3) If both A.D.H. and S.R.H. are decreased (so that G_w and E_{Na} are both low) neither pitressin nor a mineralocorticoid, administered separately, would be expected greatly to modify the pattern of excretion. This appears to be the case in iso and hypertonic saline diuresis, where the increased water excretion is not significantly inhibited either by pitressin or by deoxycorticosterone esters[4].

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Zusammenfassung

In dieser Arbeit ist eine Theorie der Nierenfunktion entwickelt worden, welche eine Wechselbeziehung zwischen den antidiuretischen und natriumretendierenden Hormonen aufzeigt. Durch diese Theorie werden einige bisher nicht verständliche Phänomene der Nierenphysiologie erklärt.

[2] R. F. PITTS and O. W. SARTORIUS, Pharmacol. Rev. *2*, 161 (1950).

[3] D. F. COLE, in preparation.

[4] W. J. O'CONNOR, Quart. J. exper. Physiol. *40*, 237 (1955). – D. F. COLE, Acta endocrin. (Kbh) *19*, 397 (1955).