Studies on Compensatory Adaptation of Renal Functions

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Changes in the excretion of water and electrolyte in one kidney after exclusion of its partner have been studied in anesthetized dogs and rabbits. Complete clamping of the contralateral kidney pedicle or ureter results in a rapid increase in the excretion of water, sodium, potassium, chloride, calcium, phosphate and bicarbonate. This response is also observed in denervated kidneys. Pretreatment with the loop inhibitor, furosemide, does not preclude adaptation which, however, is blunted by acetazolamide, an inhibitor of proximal sodium and bicarbonate reabsorption. Free-water reabsorption during hypertonic saline diuresis is normal in the remaining kidney. Compensatory adaptation, thus, appears to be located in the proximal tubule. The regulatory response to contralateral kidney exclusion is already fully developed in one-month-old rabbits. Compensatory adaptation of electrolyte excretion is not accounted for by changes in extracellular fluid volume, plasma composition, glomerular filtration rate, effective renal plasma flow, aldosterone or vasopressin.

Acute or progressive reduction of renal mass has been shown to induce adaptive changes in the remaining nephrons, so that the overall salt and water balance is well maintained. The functional adaptation that follows removal of one kidney has been studied in several species and shown to occur within the first hours following unilateral nephrectomy. Verney first reported “a rapid diuresis when renal mass was acutely reduced” [1]. The term “compensatory adaptation” was later coined by Peters, to describe the acute functional changes which follow removal of one kidney [2].

The purpose of the present experiments performed in dogs and rabbits was to further define compensatory adaptation, its mechanism and its localization along the nephron. The experimental conditions generally were the following:

— Experiments were performed on animals anesthetized with pentobarbital and connected to a respirator.
— The left kidney was eliminated by renal pedicle or ureteral ligation.
— Control experiments were performed in sham-operated animals.
— In order to keep fluid balance constant, the infusion rate of various solutions was adjusted so as to match the urine output observed in the preceding 2–3 minutes.
— ECF volume and composition were kept constant as judged by steadiness of hematocrit, plasma protein and electrolyte concentrations.
— PAH, inulin or exogenous creatinine were used as markers.
— Each animal served as its own control.

Clearance data in sham-operated animals demonstrated steady plasma conditions and excretory rates. In experimental animals, removal of one kidney did not change the plasma hematocrit, protein, Na, K or HCO₃ concentrations, thus indicating constancy of ECF distribution and composition.

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The Effect of Contralateral Kidney Exclusion on Renal Excretion in Rabbits Infused with Isotonic Saline

\( (n = 10) \)

|                      | Control       | 5 min         | 60 min        |
|----------------------|---------------|---------------|---------------|
| GFR, ml/min          | 2.58 ± 0.18   | 2.89 ± 0.19   | 3.07 ± 0.22*  |
| ERPF, ml/min         | 15.9 ± 1.4    | 18.5 ± 1.7*   | 16.3 ± 0.8    |
| V, ml/min            | 0.86 ± 0.14   | 1.11 ± 0.19** | 1.29 ± 0.18***|
| \( \text{U}_{\text{Na}} \cdot V \), amol/min | 83.8 ± 14.7   | 107 ± 21*     | 119 ± 18**    |
| \( \text{U}_{\text{K}} \cdot V \), μmol/min  | 4.2 ± 0.6     | 5.3 ± 0.7***  | 5.5 ± 0.7***  |
| \( \text{U}_{\text{Ca}} \cdot V \), μmol/min  | 1.39 ± 0.38   | 2.03 ± 0.49*  | 2.70 ± 0.51** |

Values are means ± SE. GFR, glomerular filtration rate; ERPF, effective renal plasma flow; V, urine flow; \( \text{U}_{\text{Na}} \cdot V \), \( \text{U}_{\text{K}} \cdot V \), \( \text{U}_{\text{Ca}} \cdot V \), absolute excretion rates of sodium, potassium and calcium. Control, 5 and 60 min, mean values observed during two control periods, 5 and 60 min after contralateral kidney exclusion.  

\*\( p < 0.05 \)  \quad \**\( p < 0.01 \)  \quad \***\( p < 0.001 \)

COMPENSATORY ADAPTATION OF ELECTROLYTE AND WATER EXCRETION

Pentobarbital anesthetized rabbits were infused with a Ringer's solution. After equilibration urine was collected for two control clearance periods. A snare was then tightened around the left renal pedicle or ureter, and urine collected from the right remaining kidney for the ensuing 70 minutes.

Table 1 describes the changes in water, sodium, potassium and calcium excretion observed in the remaining kidney 5 and 60 minutes after contralateral kidney exclusion. Clamping the renal pedicle was followed by a slight increase in systemic blood pressure, amounting to 5 mmHg 60 min after contralateral kidney exclusion. There was also a slight increase in GFR, but no persistent change in effective renal plasma flow.

COMPENSATORY ADAPTATION OF \( \text{HCO}_3^- \) EXCRETION

Under normal conditions, unilateral nephrectomy does not markedly disturb acid-base balance. It thus seems likely that an adaptive mechanism for acid-base regulation operates in the remaining kidney. To test this hypothesis, and to examine possible mechanisms, the functional changes immediately following contralateral kidney exclusion were studied in dogs undergoing bicarbonate diuresis. Experiments were performed on pentobarbital anesthetized dogs connected to a respirator, so that plasma pCO\(_2\) was kept constant throughout the experiment. In order to obtain plasma bicarbonate concentrations above the renal \( \text{HCO}_3^- \) threshold, hypertonic sodium bicarbonate was infused. Steady state conditions were obtained. The excretory changes following contralateral kidney exclusion are illustrated in Table 2.

The sharp and immediate increase in urine flow was accompanied by a large increase in absolute and fractional Na and \( \text{HCO}_3^- \) excretion. There was also a significant increase of K excretion. In contrast there was no change in GFR, while ERPF decreased slightly, albeit significantly, from 90.7 to 68.3 ml/min in the 60 minutes following contralateral kidney clamping. The increase in blood pressure from 103 ± 8 to 120 ± 7 mmHg was not statistically significant.

MEDIATION OF COMPENSATORY ADAPTATION

If \( \text{HCO}_3^- \) reabsorption is assumed to be mediated via a primary H ion secretion, contralateral kidney exclusion would have to depress tubular hydrogen secretion in
order to reduce bicarbonate reabsorption, a process linked in part to Na reabsorption.

To exclude the participation of aldosterone or vasopressin in these adaptive changes, experiments were performed in dogs undergoing isotonic bicarbonate diuresis, and given maximal doses of desoxycortone and vasopressin. In these dogs contralateral kidney exclusion also induced an increase in water, Na, K and HCO₃⁻ excretion from the remaining kidney. The changes were smaller but qualitatively similar to those observed in the absence of desoxycortone and vasopressin. A role of changes of aldosterone or vasopressin secretion in inducing the increase in Na, HCO₃⁻ and water excretion after contralateral kidney exclusion thus appears unlikely. In most animals, in the present investigation, exclusion of one kidney was followed by an immediate but small increase of systemic blood pressure. However this was not a consistent response and there was no clear relationship between the increase of blood pressure and the increase in fractional Na excretion. This observation agrees with Wong and Dirks' observations [4] in dogs: the excretory response to contralateral kidney exclusion was not blunted by preventing the rise in renal perfusion pressure by suprarenal aortic constriction. From the experiments reported above, it can be concluded that exclusion of one kidney induces adaptive changes in electrolyte excretion by the remaining kidney, and that these changes are not accounted for by factors known to control Na and HCO₃⁻ excretion under normal conditions.

The signal triggering compensatory adaptation does not appear to be a known physical or hormonal factor. What then is the role of renal nerves in this response? To answer this question, experiments were performed in rabbits undergoing saline diuresis. The remaining right kidney was denervated by freeing the pedicle from all connective tissue, severing all visible nerves, and painting the pedicle with lidocaine [5]. Only animals whose Na excretion from the "denervated" kidney during control periods was twice that from the opposite non-denervated kidney, were considered as adequately denervated. As in normal animals, exclusion of the contralateral kidney induced immediate excretory changes in the denervated kidney (Table 3) thus excluding a role of sympathetic nerves in this response. It is noteworthy that in this group of animals compensatory adaptation occurred without any change in systemic blood pressure.

SITE OF COMPENSATORY ADAPTATION

Compensatory adaptation could be mediated by an inhibition of electrolyte transport in the proximal tubule, or at a more distal site of the nephron. These two

|                | Control | 5 min  | 60 min |
|----------------|---------|--------|--------|
| \( P_{HCO_3} \), mmol/l | 50.5 ± 2.9 | 51.7 ± 3.2 | 51.7 ± 3.1 |
| GFR, ml/min    | 21.7 ± 2.6 | 21.9 ± 2.4 | 20.2 ± 2.3 |
| ERPF, ml/min   | 90.7 ± 14.5 | 84.4 ± 12.2 | 68.3 ± 9.1** |
| \( V \), ml/min| 3.4 ± 0.8  | 4.3 ± 1.0*** | 5.1 ± 1.0*** |
| \( FE_{Na} \), % | 12.8 ± 2.5  | 15.9 ± 3.1** | 19.5 ± 3.6*** |
| \( FE_{HCO_3} \), % | 33.7 ± 6.4  | 38.7 ± 7.1*** | 48.2 ± 8.0*** |

Values are means ± SE. \( P_{HCO_3} \), plasma bicarbonate concentration; \( FE_{Na} \) and \( FE_{HCO_3} \), fractional excretion of Na and HCO₃⁻. Other symbols as in Table 1.
The Effect of Contralateral Kidney Exclusion on Renal Excretion in Rabbits Infused with Isotonic Saline after Denervation of the Remaining Kidney

\( (n = 9) \)

|                      | Control  | 5 min     | 60 min    |
|----------------------|----------|-----------|-----------|
| GFR, ml/min          | 4.08 ± 0.46 | 4.66 ± 0.45* | 4.27 ± 0.30 |
| ERPF, ml/min         | 14.9 ± 2.7 | 16.7 ± 1.7 | 13.6 ± 1.6 |
| V, ml/min            | 0.74 ± 0.07 | 1.02 ± 0.14** | 1.15 ± 0.16** |
| FE\(_{Na}\), %        | 15.0 ± 1.9 | 17.6 ± 2.4** | 19.8 ± 2.7** |
| FE\(_{Cl}\), %        | 18.7 ± 2.5 | 22.6 ± 2.8** | 26.1 ± 3.5** |

Values are means ± SE. FE\(_{Cl}\), fractional excretion of chloride. Other symbols as in Tables 1 and 2.

possibilities were studied in dogs in which proximal or distal tubular transport was blocked before excluding the opposite kidney by continuous infusion of a diuretic [6].

In dogs given *furosemide*, an inhibitor of Na or Cl transport acting mainly along the ascending limb of Henle's loop, contralateral kidney exclusion induced a sharp increase in water, Na and HCO\(_3\), excretion, without a change in GFR. The increase in the fractional excretion of Na and HCO\(_3\), already significant 5 minutes after contralateral kidney exclusion, is illustrated on Fig. 1.

Compensatory adaptation was clearly not blunted by distal blockade with furosemide. This observation points to a proximal site for the adaptation in electrolyte excretion. This conclusion was further confirmed by pretreating dogs with *acetazolamide*, a inhibitor of bicarbonate transport acting mainly in the proximal tubule. In these dogs, contralateral kidney exclusion was not followed by any increase of urine flow, GFR, or the excretion of Na, K and HCO\(_3\) (Fig. 2).

This observations suggests that inhibition of HCO\(_3\) transport in the proximal tubule interferes with compensatory adaptation, or, in other words, that acetazolamide and compensatory adaptation depress sodium bicarbonate transport at the same level in the nephron, that is in the proximal tubule.

To further define the site of compensatory adaptation, studies were performed in rabbits undergoing progressive hypertonic saline diuresis [7]. *Free-water reabsorption* was used an an index of solute transport in the ascending limb of Henle's loop.

![Graphs](image-url)  
**FIG. 1.** Increases of fractional excretion of Na (Δ FE\(_{Na}\), %) and HCO\(_3\) (Δ FE\(_{HCO3}\), %) observed 5 and 60 min after contralateral kidney exclusion, in dogs infused with isotonic NaHCO\(_3\), and furosemide. From [6]. Reproduced by permission of the editor of the Am J Physiol
STUDIES ON COMPENSATORY ADAPTATION

The values observed in normal kidneys were compared to those observed in the remaining kidney immediately after contralateral kidney exclusion. As observed in a normal kidney, free water reabsorption in the remaining kidney bore a linear relationship to osmolal clearance, with no evidence of a limit (Fig. 3).

The regression lines in normal and remaining kidneys did not differ significantly. If anything, the slope was steeper in remaining kidneys.

This observation demonstrates that contralateral kidney exclusion does not interfere with NaCl transport in the ascending limb of Henle's loop of the remaining kidney. It suggests that the compensatory adaptation phenomenon is localised in the proximal tubule. This conclusion is supported by micropuncture studies showing a
decrease of absolute Na reabsorption in the proximal tubule of one kidney after removal of its partner [8].

DEVELOPMENT OF COMPENSATORY ADAPTATION

The response to contralateral kidney exclusion resembles in many aspects the regulation observed during isotonic saline expansion: fractional reabsorption of Na is reduced in both situations. The response to saline expansion is clearly limited in neonatal animals [9]: the developing kidney is not able to increase fractional Na excretion as well as an adult kidney in response to a saline load. What then is the response of the developing kidney to contralateral kidney exclusion?

To answer this question, ten one-month-old rabbits were studied, as previously described. As in older animals, functional removal of one kidney was followed by an immediate and progressive increase in urine flow, in Na, K and Cl excretion, without any change in GFR. One-month-old rabbits are thus perfectly able to depress Na and water fractional reabsorption after contralateral kidney exclusion, to the same extent as adult animals. Preliminary experiments in our laboratory suggest that compensatory adaptation may not be fully developed in one-week-old animals. This may be related to the relative underdevelopment of superficial nephrons in the first days of life rather than to functional immaturity.

In conclusion our studies indicate that:

1. Exclusion of the contralateral kidney induces acute compensatory excretory changes for Na, Cl, K, Ca, phosphate and HCO3 in the remaining kidney.
2. Occurrence of these changes is not mediated by changes in the circulating level of vasopressin or of aldosterone.
3. Compensatory adaptation is often accompanied, but is not dependent on changes in systemic blood pressure.
4. Exclusion of one kidney also induces compensatory adaptation in the previously denervated remaining kidney.
5. The proximal tubule appears to be the major site of compensatory adaptation.
6. The regulatory response to contralateral kidney exclusion is already fully developed in one-month-old rabbits.

While these studies, as well as others [3,10,11,12], afford some insight into the nature and site of compensatory adaptation, they fail to explain the “mechanism by which one kidney becomes cognisant of the infarction of the other and immediately responds by secreting urine at a faster rate” [1].

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