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LETTER TO THE EDITOR

Could an intrarenal Cori cycle participate in the urinary concentrating mechanism?

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In their recent study, Agarwal and colleagues showed how two forms of lactate dehydrogenase are distributed within the renal cortex and how they are affected by hypoxia (1). In the accompanying Editorial, David Sheikh-Hamad emphasized the importance of this "kidney lactate shuttle" (2). Here, we want to highlight another interesting feature of renal lactate handling that occurs in the medulla.

In the inner medulla (IM), oxygen supply is relatively poor and glucose is the major energy source. The cleavage of one glucose into two lactates produces two ATP molecules. Concentration of lactate in the IM is four- to sixfold higher than in the cortex. Countercurrent exchange between ascending (venous) and descending (arterial) vasa recta minimizes the dissipation of this concentration gradient. It has been proposed that the breakdown of glucose in the IM not only provides energy but also contributes to solute accumulation in the IM by releasing two osmotically active molecules (lactates) out of one (glucose) (3, 4). These extra solutes in the IM should help drive water from the collecting ducts.

Gluconeogenesis is known to occur in the kidney proximal tubule. It is most intense in the pars recta, a nephron segment that expresses Na^+-glucose cotransporter isoform 1 (SGLT1) in its apical membrane brush border (5). Lactate has been shown to be the preferred substrate for gluconeogenesis in the pars recta (6). It is generally assumed that the newly formed glucose is released into the peripheral blood. Could this renal-borne glucose serve some function in the kidney itself? Because SGLT1 can transport glucose in both directions (7), it is fully conceivable that this glucose could be secreted into the lumen and thus flow through the downstream nephron segments.

The efferent arterioles of the juxtamedullary glomeruli traverse the outer stripe of the outer medulla (OS) without supplying capillaries within this zone. In the OS, the blood supply of the pars recta depends almost exclusively on the numerous ascending vasa recta (AVR), which surround them closely. The pars recta and AVR share a large area of contact (Fig. 2 in Ref. 8). As explained above, AVR blood carries lactate issued from the IM. It is thus easy to assume that this lactate can be used for gluconeogenesis.

Taken together, these observations led us to propose that a Cori cycle may occur within the kidney (8). The traditional Cori cycle takes place between the liver (which produces glucose) and muscles (which consume glucose and produce lactate). In the kidney, glucose, produced by pars recta cells, may be secreted into the lumen via SGLT1 (7). Glucose may then be carried with the tubular fluid to the IM, where it will supply metabolic energy when cleaved into two lactates. Some of this lactate will be carried via the AVR to the OS, where it can be taken up by pars recta cells and used again for gluconeogenesis (6).

The mechanism allowing mammals to produce concentrated urine is not fully understood. This intrarenal Cori cycle could contribute to this urine concentrating process by converting metabolic energy, spent in the outer stripe for gluconeogenesis, into osmotic energy, released in the IM in the form of two osmoles. Moreover, the glucose present in the lumen of the loops of Henle could bring extra fuel to the thick ascending limbs in the inner stripe of the OM, if glucose can be taken up through their luminal membrane. Such a lactate-glucose-lactate cycling within the kidney allows the conversion of chemical energy, spent in the upper OM, into metabolic and osmotic energy (two ATPs plus two osmoles) delivered to the deep IM.

Lactate recycling between the renal cortex and medulla has been reported to take place in the isolated perfused rat kidney (9). Assuming that glucose produced in the pars recta may be secreted into the tubular fluid provides an explanation for the rare cases of nephrogenic glycosuria if cells in the IM and/or thick ascending limbs fail to metabolize this secreted glucose. Further studies about the fate of glucose and lactate within the kidney are required to prove or disprove this putative intrarenal Cori cycle.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

L.B. conceived and designed research; L.B. drafted manuscript; L.B. edited and revised manuscript; L.B. approved final version of manuscript.

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