phaturia[17,18] or hitherto unknown steroid-induced bicarbonaturia. If this is indeed sodium phosphaturia, then it will not be relevant to extracellular fluid volume or BP homeostasis.

In summary, Goodwin *et al.*[13] provide a convincing animal model of a common clinical condition that will be valuable for a host of further pathophysiologic studies.

DISCLOSURES

None.

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See related article, "A Critical Role for Vascular Smooth Muscle in Acute Glucocorticoid-Induced Hypertension," on pages 1291–1299.

Marconi Revisited: From Kidney to Brain—Two Organ Systems Communicating at Long Distance

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In this issue of *JASN*, Liu *et al.*[1] demonstrate in an animal model that acute kidney injury (AKI) is related to anatomic lesions and functional disturbances of the brain. This connection seems linked in part to inflammation. Inflammatory markers are increased after AKI not only in serum and kidneys but also in brain. Such long-distance interorgan cross-talk is observed for heart and lungs[2–4] as a result of the release of humoral factors generated in damaged kidneys that seep into blood. In the case of the brain, however, the mechanism might be more complex, because the brain-blood barrier (BBB) normally interferes with trespassing substances.

The existence of a link between inflammation and the brain has been suggested previously regarding development of fever and so-called "sick behavior."[5] The brain lesions observed after AKI[1] seem more severe and more definitive (with pyknosis and cell death) *versus* what is observed in mere sick behavior. Probably damage to the kidney triggers more profound mechanisms because a vital organ is affected and a larger number of messengers are released. Uremic encephalopathy in AKI usually presents in a dramatic way with a fast progression from mild sensorial clouding to delirium and coma.[6]

How is it possible that distant inflammation affects the brain? Several different mechanisms are possible[5,7]: Cytokines

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may circumvent the BBB, affecting brain zones where the BBB is more penetrable, such as circumventricular structures, and may there bind to innate brain macrophages or other immune cells and activate them; cytokines may activate brain endothelial cells, which can pass the message to inflammatory cells across the BBB; cytokines may activate white blood cells, which adhere to brain endothelia and pass their message through the endothelia to the other side; communication may occur directly through neuronal pathways, such as the vagal nerve; transfer of message may occur through noncytokine messengers, such as prostaglandins, which are smaller than the cytokines, so they more easily penetrate the BBB; and the efficacy of the BBB may be altered during inflammation.

A second pathway for distant brain damage in the presence of AKI could be uremic solute retention, which in turn triggers a whole cascade of both neuronal cell damage and proinflammatory reactions. A host of uremic compounds are retained in uremia, and several of them exert a deleterious effect on several organ systems,[8] including the central nervous system.[9] Several protein-bound compounds change endothelial cell function and permeability[10] and in this way may contribute to the modification of the BBB. In addition, other compounds activate white blood cells and because of their molecular weight or other characteristics may cross the BBB more easily than the cytokines. Compounds with low molecular weight, such as several of the guanidines[11] and the phenolic compound p-cresylsulfate,[12] have immune-stimulating properties that might exert this activity on both sides of the BBB, especially if the permeability of the latter is affected by inflammation or uremia. Of note, the phenolic compound quinolinic acid, which is a retained uremic solute,[8] is also linked to neurotoxicity.[13,14] Likewise, indoxylsulfate, another protein-bound uremic solute belonging to the group of indoles, is linked to central nervous system toxicity in cis-platinum–induced AKI.[15] In a comprehensive analysis of the acute effects of 17 candidate uremic neurotoxins on murine spinal cord neurons in primary, dissociated cell cultures, some compounds (guanidinosuccinate and spermine) display neuroexcitatory effects that are mediated by calcium channels.[16]

Brain leukocytes might also be primed for further activation in case of concomitant conditions, such as already present disease or inflammation. Because AKI frequently develops after sepsis or together with other comorbidities, brain damage might even be worse *in vivo* than in the relatively "clean" model of pure ischemia-reperfusion, as in the study by Liu *et al.*[1]

Bidirectional cross-talk between kidneys and other organs is also possible—that is, other organs may in turn affect kidney function.[17] Brain lesion resulting in renal effects is repeatedly observed with cadaveric kidneys harvested from donors with brain death[18,19] and might involve catecholamines and inflammatory messengers. Hence, such bidirectional effects may also play a role in AKI.

It would be interesting to discern whether the observed effects are attributable to kidney injury *per se* or merely to inflammation. As a "control" experiment, a model of acute liver injury was evaluated by Liu *et al.*,[1] resulting in modest brain lesions and less inflammation. No other control model of inflammation (*e.g.*, administration of LPS) was included in the study. Likewise, if the "uremic toxin" hypothesis is correct, then brain damage would be comparable in the ischemic and bilateral nephrectomy models. Unfortunately, separate data on anatomic brain damage in bilateral nephrectomy are not reported by Liu *et al.*[1]; therefore, the question of whether the brain lesions are linked to systemic inflammation or to kidney injury *per se* remains unanswered.

Finally, one should be careful in extrapolating animal findings to the human condition.[20] Nevertheless, unraveling the mechanisms at play might be helpful in developing preventive measures, such as blocking inflammatory events or other mechanisms, or starting renal replacement strategies earlier. Finding adequate means to cope with brain injury might not only create a benefit for the central nervous system in AKI but also disentangle a vicious loop, if brain lesions in their turn would affect kidney function.

DISCLOSURES

None.

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See related article, "Acute Kidney Injury Leads to Inflammation and Functional Changes in the Brain," on pages 1360–1370.

Diabetes after Transplantation and Sirolimus: What's the Connection?

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New-onset diabetes is a common complication of renal transplantation. The appearance of this form of diabetes is associated with worsening cardiovascular risk and loss of renal allograft function.[1–3] The most important modifiable risks for its appearance are obesity and the choice of immunosuppressant drugs. In a landmark study, Kasiske *et al.*[2] used data from the US Renal Data System and Medicare billing to show the high incidence of diabetes after transplantation is associated with choice of initial maintenance immunosuppression, as well as race, ethnicity, obesity, and history of hepatitis C infection. More important, they found diabetes is a strong, independent predictor of graft failure and mortality. The incidence of new diabetes was higher in patients treated with tacrolimus, confirming an association seen in one of the earliest tacrolimus studies published in 1997.[4] In that study, the initial incidence of diabetes (defined liberally as the use of insulin for ≥30 d in patients with no history of diabetes) was 19.9% in tacrolimus-treated patients and 4% in cyclosporine-treated patients. Of the 36 patients who developed diabetes, seven tacrolimus-treated patients and one cyclosporine-treated patient were able to discontinue insulin treatment within the first year. Five of the tacrolimus-treated patients were weaned from insulin without discontinuing tacrolimus or steroid therapy, and two patients discontinued insulin after crossover to cyclosporine. It is important to note that discontinuation of insulin is not the same as return to normoglycemia. As Crutchlow and Bloom[5] pointed out, the term "transplant-associated hyperglycemia" encompasses all types of abnormal glucose homeostasis after transplantation.

In this issue of *JASN*, Johnston *et al.*[6] analyzed data from >20,000 kidney transplant recipients in the US Renal Data System database for associations between particular drug regimens and diabetes. Using an analysis of multiple drug combinations, they found combinations that include sirolimus are also associated with more Medicare billing for diabetes than are drug combinations without sirolimus. The most diabetogenic combination on the basis of these results is the combination of sirolimus and a calcineurin inhibitor. The authors analyzed a subgroup of recipients (n = 16,861) who did not change their immunosuppressive regimen during the first posttransplantation year and found that regimens including sirolimus have an association with diabetes only in the presence of a calcineurin inhibitor. Their analysis did not address the role of induction therapy in the development of diabetes.

These new data do not confirm clinical findings from initial sirolimus studies, and, as Johnston *et al.*[6] points out, previous studies on sirolimus-induced diabetes were mixed in their results. Ordinarily this would cast some uncertainty as to the interpretability of all of these findings; however, a growing body of evidence suggests that chronic inhibition of mammalian target of rapamycin (mTOR) with sirolimus leads to exacerbation of hyperglycemia and insulin resistance. Normal sig-

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