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Review Article

Brain-kidney cross-talk: Definition and emerging evidence☆,☆☆

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ABSTRACT

Cross-talk is broadly defined as endogenous homeostatic signaling between vital organs such as the heart, kidneys and brain. Kidney–brain cross-talk remains an area with excitingly few publications despite its purported clinical relevance in the management of currently undertreated conditions such as resistant hypertension. Therefore, this review aims to establish an organ-specific definition for kidney–brain cross-talk and review the available and forthcoming literature on this topic.

1. Introduction

Normal renal function mediates whole-body homeostasis, including neuronal homeostasis [1]. Renal insufficiency incites central and peripheral nervous system derangements in multiple patterns, such as cognitive decline (denoting global cerebral dysfunction), cerebrovascular events (denoting focal cerebral dysfunction possibly arising from vasculitis), and peripheral neuropathy (raising consideration of mixed effects on central neuroglia versus peripheral Schwann cells). Moreover, the treatment for chronic kidney disease (CKD), hemodialysis (HD), has been associated patterns such as dialysis disequilibrium (suggesting either cerebellar dysfunction or posterior infratentorial vasculitis) and dialysis dementia (suggesting global cerebral cortex dysfunction).

The vectors of cross talk are thought to include hormones (endocrine-mediated cross-talk), baroreceptors and osmoreceptors (sensor-mediated cross-talk [2]), and direct inter-organ innervation (neuron-mediated cross-talk, possibly disrupted after kidney transplant via autonomic Wallerian degeneration).

As the population of patients with renal insufficiency continues to grow, this topic will rise in importance [3] as efforts are undertaken to reduce cognitive decline (which is often associated with increased health care costs later in life). This report aims to discuss our current understanding of signaling mechanisms ("cross-talk") that may underlie these pathophysiological observations.

2. Physiologic rationale of cross-talk between the kidney and brain

Homeostatic collaboration between the kidneys and brain has been purported via the following pathways:

Normal blood tonicity regulation. Antidiuretic hormone is an endocrine brain-kidney cross-talk mechanism. The kidneys adjust sodium/water balance. The hypothalamus generates antidiuretic hormone (ADH) and releases it via the posterior pituitary gland [4]. Cardiovascular baroreceptors and hypothalamic osmoreceptors mediate the pathway. Homeostasis is restored by the combination of renal water retention induced by ADH, the effect of aldosterone on renal sodium retention, and concomitant mobilization of sodium from body stores (particularly the ions that are bound to proteoglycans in the interstitial matrix and muscles) [5]. ADH acts via its receptors (AVP receptors), mostly V2 receptors in the renal collecting duct; binding of ADH to these receptors leads to both increased number and synthesis of aquaporin 2 channels in the apical membrane, causing water reabsorption by the kidney [6]. In the brain, there are mostly aquaporin 4 water channels controlling water movement between plasma, cerebrospinal fluid, interstitial matrix and neurons/glial cells,

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particularly astrocytes. As a response to change in cerebral extracellular tonicity, cellular adaptation occurs to maintain cell size and membrane structure with the change in the number of aquaporin 4 water channels respectively [5]. Disturbance of these mechanisms lead to some syndromes such as diabetes insipidus and syndrome of inappropriate ADH secretion (SIADH).

Normal blood pressure regulation. The sympathetic nervous system mediates renal tubular water and sodium reabsorption at the level of the nephron to affect sodium/water balance. Sympathetic nerves also alter renal blood flow and glomerular filtration rate via renal vasoconstriction and alterations in the renin-angiotensin aldosterone system (RAS). The loop is completed by afferent renal nerves that ascend to the central nervous system (CNS) to modulate central sympathetic and parasympathetic outflow [7]. In the normal state, renal afferent sensory activity leads to a reflex decrease in sympathetic outflow, which is known as an inhibitory reno-renal reflex [8]. The reno-renal reflex is impaired in hypertension, and an increase in renal afferent activity augments the sympathetic excitation to the kidney and aggravates hypertension [9].

3. Pathologic mechanisms of dysregulated cross-talk between the kidney and brain

Disease states are thought disrupt kidney–brain cross-talk via the following purported mechanisms:

1. ***Electrolyte-mediated brain edema***. Renal dysfunction leads to electrolyte imbalance [10]. In turn, electrolyte imbalances are propagated through the blood brain barrier to enact brain edema. The distribution is generalized throughout the brain, leading to general brain dysfunction (somnolence, seizures, coma). Furthermore, vascular dysregulation can lead to intracranial hemorrhage which can be life threatening. Furthermore, the rapid correction of electrolyte imbalances can lead to such conditions as central pontine myelinolysis.
2. ***Autoregulatory failure***. Patients with CKD have impaired autoregulatory reserve [11] further compounded autonomic dysfunction (specifically, baroreflex insensitivity [12]). Stage V CKD patients are therefore less able to buffer the hemodynamic changes induced by HD and experience greater reductions in both systolic and diastolic blood pressures during HD [13]. Autoregulation is further hindered by the endothelial dysfunction in this population [14].
3. ***Neurotoxin accumulation***. CKD leads to accumulation of various uremic toxins, including guanidine compounds [15], that may play a role in the development of encephalopathy. Of note, patients with AKI are more susceptible to encephalopathy than those with chronic kidney disease, probably because there is less time to adapt to uremia.
4. ***Inflammatory pathway activation***. The central nervous system, once believed to be immunologically isolated, is now known to generate and respond to cytokines at both glial and neuronal levels. Specifically, AKI causes hippocampal inflammation and is associated with hippocampal neuronal death [16]. Moreover, AKI resulted in generalized astrocyte activation and increased cerebral pro-inflammatory mediators [17].
5. ***Increased permeability of the blood brain barrier and brain cerebrospinal fluid barrier***. AKI increases blood brain barrier (BBB) permeability, further facilitating passage of the aforementioned neuroinflammatory milieu [16] [18,19]. It is known that the intact BBB and BCSFB (brain cerebrospinal fluid barrier) play a major role in regulating the transport of amino acids, proteins, and essential nutrients into and out of the brain.
6. ***Intercellular junctional dysfunction***. Toll-like receptors (TLRs) on microglia, astrocytes, neurons, and endothelial cells play a role in neuronal injury, apoptosis and expression of cytokines, such as tumor necrosis factor (TNF), interleukin-6 (IL-6), inducible nitric oxide synthase (iNOS), and interferon (IFN)-γ [20,21]. These cytokines not only augment ongoing inflammation but mediate aquaporin expression (especially type 4 aquaporin) resulting in water influx and brain edema [1]. This leads to a positive feedback loop of brain injury, TLR dysfunction, osmotic disruption that repeats brain injury.
7. ***Reactive oxygen and reactive nitrogen species***. AKI generates reactive oxygen species and reactive nitrogen species. This oxidative stress increases the susceptibility of brain tissue to ischemic damage, for example by resulting in increased permeability of the BBB, which can lead to brain edema, hemorrhage, inflammation, and ischemia–reperfusion injury [22,23].
8. ***Uremic encephalopathy***. Chronic renal insufficiency leads to accumulation of metabolites, hormonal disturbances, altered metabolism, and imbalances in excitatory and inhibitory neurotransmitters [24]. Chronic uremia is further known to disrupt amino acide metabolism, for example, reduced concentrations of large neutral and branched chain amino acids are seen in the cerebrospinal fluid (CSF) [25] whereas CSF levels of free tryptophan and 5-hydroxytryptamine levels are increased [26].
9. ***Hyperparathyroidism***. Secondary hyperparathyroidism increases cerebral gamma-Aminobutyric acid (GABA) levels. Moreover, animal studies have shown that parathyroidectomy restores function of pathways mediating release, reuptake and degradation of noradrenaline and acetylcholine [27,28]. Elevated fibroblast growth factor 23 (FGF-23) levels [29], low vitamin D levels [30], and increased asymmetric dimethylarginine (ADMA) [31] were suggested as causative factors for cognitive dysfunction. ADMA has also been implicated for depression and behavioral changes in CKD patients [32].
10. ***Adverse drug reactions and polypharmacy***. Renal clearance-dependent medications such as penicillin, cephalopsporins and antiviral agents (acyclovir) can accumulate and cause encephalopathy independently or via polypharmacy [33,34].
11. ***Metabolic acidosis***. Renal insufficiency promotes an acidic environment in which protons can activate acid-sensing ion channels resulting in cellular influx sodium and calcium. This leads to cell membrane depolarization, cellular injury, and potentially cell death [35].
12. ***Dialysis-induced fluid shifts***. Rapid hemodialysis reduces plasma water tonicity via urea removal. Because urea transport through cell membranes is limited compared to water transport, a urea concentration gradient develops between the plasma water and both the cerebrospinal fluid and cerebral interstitium. This causes water movement into the brain and results in brain swelling [10]. Care is therefore required to adjust the dialysis prescription to minimize the changes in plasma tonicity during hemodialysis treatment [36].
13. ***Hypovitaminosis***. CKD depletes intracellular levels of folate and thiamine [37] and purports aberrant nitric oxide metabolism [38], which can increase susceptibility to cerebral infarction and has been associated with cerebral white matter lesions.
14. ***Brain-to-kidney dysautonomia***. Sympathetic and parasympathetic outflow to the kidneys can become deranged by the aforementioned mechanisms, leading to renal blood flow and glomerular filtration derangements [16].
15. ***Systemic inflammatory response***. Severe brain injury is known to trigger multiorgan immunologic consequences. As a result, it has been shown that donor brain death negatively impacts allograft success rates due to immunologic rejection [39,40]. Fig. 1 diagramatically outlines these mechanisms.

4. Connecting health and disease: using cross-talk in the clinic

4.1. Neurocognitive decline in patients with renal insufficiency

Gradual cognitive decline will typically be the first clinical sign of deranged kidney–brain cross-talk. Specifically, independent of other

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