Strangers on a Train*: atypical glutamate receptors in the kidney glomerulus. Focus on “Functional NMDA receptors with atypical properties are expressed in podocytes”

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JUST MORE THAN A DECADE AGO, a fascinating cell type of the kidney glomerulus was catapulted into the focus of kidney research. Landmark genetic studies identified gene defects of kidney podocytes as cause of proteinuria and end-stage renal failure (1, 12, 14, 27) and initiated a new spurt of research that profoundly changed our understanding of the glomerular filtration barrier of the kidney (13). Podocytes are the visceral epithelial cells of the kidney glomeruli, small microvascular units that are required for filtration of plasma water and the production of urine. Neighboring podocytes elaborate long, regularly spaced, interdigitated foot processes that enwrap the glomerular capillaries and form a 40-nm wide filtration slit bridged by a membrane-like cell contact, the slit diaphragm. Together with fenestrated endothelial cells in the glomerular capillaries and the glomerular basement membrane that separates these two communicating cell types, podocytes form the kidney filtration barrier (8, 19). About a million glomerular microvascular beds are responsible for the filtration of 180 liters of primary urine every day. In doing so, the filtration barrier behaves as a selective sieve, restricting the passage of macromolecules on the basis of their size, shape, and charge (8). Thus the intact kidney filtration barrier tightly restricts passage of proteins based on their biophysical properties resulting in an almost protein-free filtrate. When podocytes are injured, the intercellular junctions and cytoskeletal structure of the foot processes are altered, and the cells take on an “effaced” phenotype (15, 17). Typical slit diaphragm structures disappear and proteinuria develops. This often results in progressive renal damage and life-threatening renal failure.

Although deriving from a uniform group of epithelial precursor cells, podocytes have a limited capacity of self-renewal and display very unique properties that partially resemble those of neurons (20). Akin to neuronal processes the podocyte primary extensions are based on a microtubular cytoskeleton, whereas the secondary processes, which are largely identical to the dendritic spines of neurons, are structured through actin cytoskeletal networks (4).

The article by Anderson and colleagues (1a) point toward another parallel of these two cell types: Podocytes contain functional N-methyl-D-aspartic acid (NMDA) receptors, a system of molecules that act as molecular devices for controlling synaptic plasticity and memory function in the brain. NMDA receptors are cation channels gated by glutamate, the main excitatory neurotransmitter in the mammalian central nervous system (2). NMDA receptors comprise a class of ionotropic glutamate receptors that also includes α-amino-3-hydroxy-5-methyl-4-isoxazole-propionate (AMPA) receptors and kainate receptors. The names of these subclasses are derived from the selective synthetic agonists that can be used to distinguish them. NMDA receptors are heterotetrameric complexes composed of NR1 and NR2 subunits (2). Subunit composition governs the biophysical properties and physiological functions of these ionotropic receptors. NMDA receptors serve a multitude of functions. They generate rhythms for breathing and locomotion and control the processes underlying learning, memory, and neuroplasticity (18). Consequently, abnormal expression levels and altered NMDA receptor function have been implicated in several neurological disorders and pathological conditions. Reduced NMDA receptor function can result in cognitive defects, whereas overstimulation causes excitotoxicity and subsequent neurodegeneration (9). NMDA receptors are also expressed in several nonneuronal tissues where their properties and physiological functions are poorly understood.

In their interesting study, Anderson et al. show that NMDA receptors are expressed and functional in podocytes. Sustained stimulation of the receptors resulted in activation of mitogen-activated protein kinases and the small G protein RhoA in podocytes. The authors also analyzed the pharmacological and biophysical properties of the podocyte NMDA receptors and found that in broad outline, they are similar to their neuronal counterparts. However, one rather peculiar difference may have important implications. The podocyte receptors do not respond to L-glutamate or L-aspartate. This surprising finding contrasts the recent hypothesis that a local glutamatergic signaling system similar to the one found in neurons may operate in podocyte secondary processes (6, 22). From the new data it is interesting to note that numerous podocyte proteins may have a dual role in the kidney and brain. In mouse genetic experiments mammalian Neph proteins were first identified as podocyte proteins. Genetic deletion of Neph1 resulted in severe podocyte abnormalities and kidney failure (3). However, Neph1 and its siblings Neph2 and Neph3 are also highly expressed in the developing brain (5). Although their role in mammalian brain development is not yet clear, data from Caenorhabditis elegans and Drosophila melanogaster suggest that Neph may have important roles in synapse targeting and wiring the brain (21, 25, 26). Intriguingly, Neph proteins also interact with PICK1 in podocytes and neurons (T. Benzing,

* Strangers on a Train is the 1951 movie directed by Alfred Hitchcock.

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unpublished observations). PICK1, a BAR-domain containing adapter protein, was originally identified as a major regulator of NMDA receptors in neurons, further supporting the podocyte-neuron relationship (7, 28). NMDA receptors and PICK1 cooperate to regulate neuronal process shape and morphology, which may also occur for their counterpart in podocyte foot processes (23).

The characterization of functional NMDA receptors raises many questions that remain unanswered: Which ligand triggers NMDA receptor activation in podocytes? What is the subunit composition of NMDA receptors in podocytes that determines their unique properties? Does NMDA signaling have a role in regulating the ultrastructure of podocytes? Might NMDA receptors be part of a regulatory circuit that controls glomerular hemodynamics and/or filtration rate? It has been speculated that podocyte signaling may be important in controlling the glomerular microvasculature (10, 24). Compelling evidence suggests a role for slit diaphragm proteins in mechanosensation at the kidney filtration barrier (11). Thus it is tempting to speculate that NMDA receptors may operate in a neuron-like circuit that responds to mechanical strain and controls glomerular hemodynamic or filtration rate.

In addition to these physiological functions, it is conceivable that glomerular NMDA receptors are also critical in pathophysiological settings. Blocking of NMDA receptors has been reported to improve renal function after ischemia or toxic injury (16, 29). However, whether hyperactivation of NMDA receptors may damage podocytes through mechanisms akin to excitotoxicity or through more subtle alterations, such as reduction in nephrin expression, as demonstrated by Anderson and colleagues (1a), remains unclear. Although all these and other questions remain unanswered, the study by Anderson et al. provides a strong impetus for addressing these issues in greater detail. Armed with this knowledge the functional relevance of NMDA receptors now needs to be studied in vivo.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

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