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Review Article

A possible mechanism for the progression of chronic renal disease and congestive heart failure

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Abstract

Chronic neurologic diseases such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis, as well as various forms of chronic renal disease and systolic congestive heart failure, are among the most common progressive degenerative disorders encountered in medicine. Each disease follows a nearly relentless course, albeit at varying rates, driven by progressive cell dysfunction and drop–out. The neurologic diseases are characterized by the progressive spread of disease–causing proteins (prion–like proteins) from cell to cell. Recent evidence indicates that cell autonomous renin angiotensin systems operate in heart and kidney, and it is known that functional intracrine proteins can also spread between cells. This then suggests that certain progressive degenerative cardiovascular disorders such as forms of chronic renal insufficiency and systolic congestive heart failure result from dysfunctional renin angiotensin system intracrine action spreading in kidney or myocardium. J Am Soc Hypertens 2015;9(1):54–63.

Keywords: Intracrine; neurodegenerative diseases; the renin-angiotensin system.

Background

Many apparently non–infectious chronic illnesses demonstrate a clinical course characterized by progressive organ dysfunction and cell loss. For example, neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and others typically progress over years to decades as cells become dysfunctional and die.[1,2] Similarly, systolic congestive heart failure is characterized by a progressive loss of cardiac contractility associated with cardiomyocyte drop out.[3] And it is well known that chronic renal insufficiency, be it the result of diabetes, hypertension, or other factors, follows a progressive downhill course in spite of the best available therapy.[4,5] This kind of progression is characteristic of infectious and neoplastic diseases, although in those cases, the time course of progression is, in general, more rapid than in the above cardiovascular and neurologic disorders. However, it has become apparent that in the case of the neurodegenerative disorder Creutzfeldt–Jakob disease (CJD), as well as bovine encephalopathy (mad cow disease), kuru, and a variety of other so–called prion diseases, an infectious protein unassociated with nucleic acid is the likely causative agent, capable of spreading between individuals on contaminated neurosurgical instruments and capable of spreading through the nervous system by an essentially infectious process.[1,2] Bovine encephalopathy and kuru have an even more obvious infectious capability demonstrated by spread to humans via consumption of infected tissue. The proteinaceous infectious particles involved in these disorders (prions) are mis–folded normal proteins that produce disease in target cells by inducing a mis–folding of their normal homologues in those cells (along with secondary aggregation of mis–folded prions), resulting in trafficking, by one mode or another, of the newly created mis–folded protein to nearby cells, intracellular aggregation of the prion protein, and cell death. Of note, several neurodegenerative disorders that are apparently not easily transmissible between individuals, do nonetheless exhibit the intercellular spread of mis–folded prion-like proteins that produce aggregation and progressive disease. Included in this category are Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and others.[1,2] This then suggests the possibility that a similar process could be operative in non–neurologic chronic degenerative diseases and, in particular, in systolic congestive heart failure (CHF) and chronic renal failure (CRF).

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This proposal at first seems unlikely to be correct. Although CHF and CRF are progressive, there is no evidence of a transmissible agent operative in either of them. Rather progression seems to result from the persistence of an underlying cause—for example, ongoing ischemia in the case of CHF, and diabetes or hypertension in the case of CRF—coupled with one or more secondary physical or pathogenic factors—for example, ventricular dilatation in the case of CHF and glomerular hypertension and hyperfiltration in the case of CRF—that perpetuate tissue stress and continued cell loss. Physical processes and disease–associated pathophysiologic factors seems to produce progression, not a quasi–infectious agent. Also, the fact that renal function normally declines with age suggests the possibility that progressive renal disease represents an acceleration of an expected decline in function. Finally, while the progression of the prion–like neurodegenerative diseases appears to depend on the inter–neuronal spread of prion–like proteins, the initiating cause of these diseases can be genetic (usually involving the overproduction of normal prion–like protein that increases the chance of random mis–folding, or the synthesis of an abnormal aggregation–prone form of the protein), infectious, or environmental, as in the case of neurotoxin exposure and Parkinson's disease. In the case of CHF and CRF, initiating causes are more clearly defined. Moreover, interventions directed against those causes and the physical and physiological factors associated with progression have been shown to ameliorate disease. For example, glucose and blood pressure control are beneficial in CRF, and renin angiotensin system (RAS) blockade is partially effective in both CRF and CHF secondary to systolic dysfunction, although in spite of considerable effort, attempts at halting disease progression by modifying these pathophysiological factors have not been successful.[3–5] At the same time, the partial effectiveness of RAS blockade in these cardio–renal disorders could point to a nexus between the protein components of the RAS and prion–like proteins.

Signaling Proteins and Chronic Disease Progression

Just as prions and prion–like proteins can spread between cells, be internalized, and act in cell interiors, so also can many physiological signaling proteins and peptides. These moieties, called intracrines, can traffic between cells either following secretion, atypical secretion, via exosomes, or possibly even via nanotubes.[6–12] They can signal at classical cell surface receptors or after internalization, and their intracellular signaling can be non–canonical—that is, independent of classical receptors—or canonical—mediated by classical receptors located in the intracellular space.[12] Some intracrines (for example, parathyroid hormone–related protein, PTHrP) also function in their cells of synthesis, and in that circumstance, frequently one or more intracrine transcripts lacks a secretory signal, and therefore, its product is retained within the cell, while other transcripts encode proteins that are secreted. Intracrines, while sharing these common functionalities, are structurally diverse: hormones, growth factors, cytokines, DNA binding proteins, and enzymes, among other moieties, can act in an intracrine mode. Also of note, these signaling proteins, when acting in target cells, often up–regulate their own synthesis or that of their signaling cascades and thereby produce a feed–forward loop that produces what might be called an active form of differentiation in target cells: the action of the up–regulated internalized intracrine renders the cell in a new state of responsiveness/differentiation that persists even when extracellular intracrine is no longer present.[6–12] For example, homeodomain transcription factors can be secreted by cells, taken up by target cells, up–regulate their own synthesis, and then spread from cell to cell. This kind of active differentiation has been reported for the homeodomain proteins PDX1 and Pax6, although virtually all homeodomain proteins contain an internalization signal and are intracrine.[13,14]

There are similarities between the action of the prion–like proteins involved in neurodegenerative disorders and intracrines.[15] Indeed, the normal forms of some prion–like proteins function as intracrines under normal physiological circumstances. For example, native alpha–synuclein, the protein which in a mis–folded form is a prion–like protein involved in Parkinson's disease, is an intracrine: it traffics between cells; after internalization, it traffics in the intracellular space to microtubules, nucleus, and mitochondria; it has physiologic functions in target cells after internalization. The intracrine–like properties of prion–like proteins have already been touched on: they can traffic between cells after secretion, release from dead cells, or via exosomes or nanotubes; they are internalized by target cells where they produce disease because of one or another aberrant function usually involving aggregation.[8,15] There is some evidence of up–regulation of the underlying normal protein form as a means of enhancing disease propagation. These observations further suggest a nexus between the pathogenic mechanism involved in prion–like neurodegenerative disorders and intracrine functionality.[15] They further raise the possible that intracrines, many of which are active in cardiovascular disease, could, either as result of their normal function or of abnormal action, produce progressive disease in CHF, CRF, and possibly other cardiovascular disorders. The RAS is an exemplar of a possible link between intracrine biology and progressive cardiovascular disease.

The RAS and Progressive Disease

It is well established that inhibitors of angiotensin II action, be they converting–enzyme inhibitors or AT1 receptor blockers (ARBs), blunt cardiac left ventricular hypertrophy, diminish inappropriate ventricular dilatation following