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Angiotensin II receptors and peritoneal dialysis-induced peritoneal fibrosis

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ABSTRACT

The vasoactive hormone angiotensin II initiates its major hemodynamic effects through interaction with AT1 receptors, a member of the class of G protein-coupled receptors. Acting through its AT1R, angiotensin II regulates blood pressure and renal salt and water balance. Recent evidence points to additional pathological influences of activation of AT1R, in particular inflammation, fibrosis and atherosclerosis. The transcription factor nuclear factor κB, a key mediator in inflammation and atherosclerosis, can be activated by angiotensin II through a mechanism that may involve arrestin-dependent AT1 receptor internalization.

Peritoneal dialysis is a therapeutic modality for treating patients with end-stage kidney disease. The effectiveness of peritoneal dialysis at removing waste from the circulation is compromised over time as a consequence of peritoneal dialysis-induced peritoneal fibrosis. The non-physiological dialysis solution used in peritoneal dialysis, i.e. highly concentrated, hyperosmotic glucose, acidic pH as well as large volumes infused into the peritoneal cavity, contributes to the development of fibrosis. Numerous trials have been conducted altering certain components of the peritoneal dialysis fluid in hopes of preventing or delaying the fibrotic response with limited success.

We hypothesize that structural activation of AT1R by hyperosmotic peritoneal dialysis fluid activates the internalization process and subsequent signaling through the transcription factor nuclear factor κB, resulting in the generation of pro-fibrotic/pro-inflammatory mediators producing peritoneal fibrosis.

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1. Introduction

The heptahelical G protein-coupled receptors (GPCRs) are the largest and most diverse superfamily of cell surface receptors, with nearly 800 human genes encoding full-length GPCRs (Lander et al., 2001; Venter et al., 2001). Their evolutionary diversity permits GPCRs to detect an extraordinary array of extracellular stimuli, from neurotransmitters and peptide hormones to odorants and photons of light. GPCRs function in neurotransmission, neuroendocrine control of physiologic homeostasis and reproduction, regulation of hemodynamics and intermediary metabolism, and control the growth, proliferation, differentiation, and death of cells. Not surprisingly then, GPCRs are the single most common target of drugs in clinical use (Flower, 1999).

Nearly all GPCRs act as ligand-activated guanine nucleotide exchange factors (GEFs) for heterotrimeric G proteins. Activated GPCRs catalyze GTP for GDP exchange on heterotrimeric G protein Gα subunits, promoting dissociation of the GTP-bound Gα subunit from the Gβγ subunit heterodimer. In turn, free Gα-GTP and Gβγ subunits regulate the activity of enzymatic effectors, such as adenylate cyclases, phospholipase-C isoforms, and ion channels, generating small molecule second messengers that control the activity of key enzymes involved in intermediary metabolism. Additionally, GPCRs are capable of generating signals that are independent of their intrinsic GEF activity by 'coupling' to adapter or scaffold proteins that link the receptor to novel, non-G protein-regulated, effectors (Luttrell, 2006). Among these non-G protein effectors are the arrestins, cytosolic proteins that mediate GPCR desensitization and internalization by binding ligand-activated GPCRs, uncoupling them from their cognate G proteins, and tar-

Abbreviations: AT1R, angiotensin II receptor; β-Arr, beta-arrestin; NF-κB, nuclear factor κB; TGF-β1, transforming growth factor β1; GPCRG, protein-coupled receptor; ESRD, end-stage renal disease; PD, peritoneal dialysis; ARBs, angiotensin II receptor blockers.

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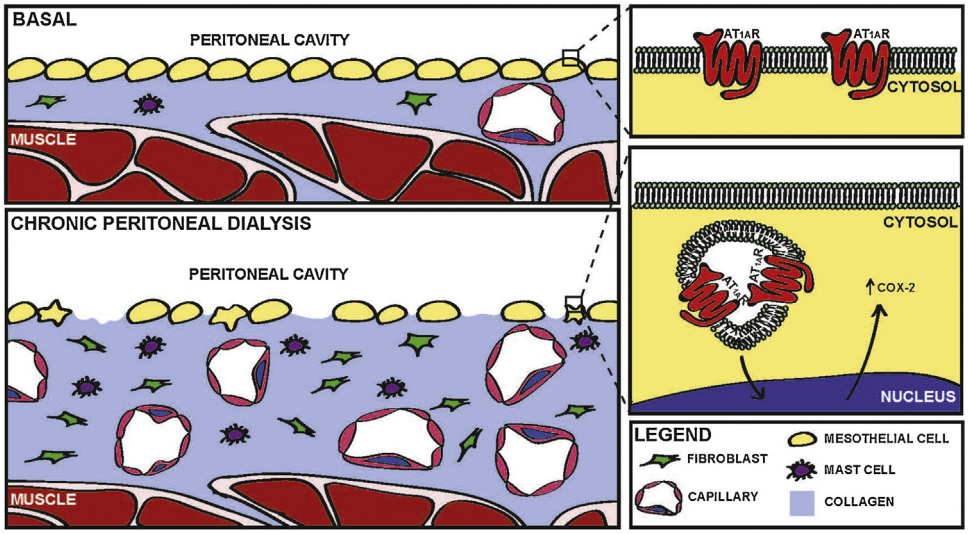

Fig. 1. Effects of chronic PD on sub-mesothelial morphology of the peritoneal cavity. Under basal conditions, peritoneal mesothelial cells (PMC) form a continuous monolayer of cells forming a permeability barrier between the fluid of the peritoneal cavity and the submesothelial capillary bed. Under basal conditions, AT1Rs of PMC reside in the cellular plasma membrane (see inset). The submesothelial matrix composed mostly of collagen 1, includes few fibroblasts, mast cells and capillaries. Chronic PD results in disruption of the PMC monolayer, a breakdown in the permeability barrier, influx of mast cells and fibroblasts and an increase in extracellular matrix accumulation and increase in capillary number. Under these conditions, we hypothesize that the hyperosmotic PD fluid promotes the internalization of AT1Rs into cytosolic endosomes (see inset) promoting activation and nuclear localization of NF-κB (see Fig. 3).

geting them to clathrin-coated pits. The arrestins also function as ligand- regulated scaffolds bringing catalytically-active cargo proteins into GPCR-based 'signalsome' complexes that regulate non-receptor tyrosine kinase activity, mitogen-activated protein (MAP) kinase cascades, protein ubiquitination/deubiquitination, pro-survival Akt signaling, nuclear factor κB (NF-κB) signaling, and cytoskeletal rearrangement/cell motility (Luttrell and Gesty-Palmer, 2010). It is increasingly recognized that these non-canonical forms of GPCR signaling contribute to both physiologic and pathophysiologic processes, among them cell proliferation, non-proliferative cell growth, survival and apoptosis, cell migration, chemotaxis and secretory function (Luttrell, 2013).

Not only is downstream GPCR signaling far more diverse than originally envisioned, the process of receptor activation is itself subject to extensive, and often tissue-specific, modulation. Rather than behaving as simple binary switches whose transition between 'on' and 'off' states is determined by the local concentration of agonist, GPCRs adopt multiple conformationally discrete 'active' states that vary in the efficiency with which they promote receptor coupling to different downstream effectors (Gesty-Palmer and Luttrell, 2011). Moreover, anything that comes into contact with the receptor, whether a ligand, another protein, or lipid in the membrane, may influence the receptor's conformational ensemble in a way that impacts signaling. It is clear that differences in orthosteric ligand structure can introduce 'bias' into receptor coupling, so as to favor coupling to some downstream effectors over others. Protein-protein interactions that modify signaling include the formation of GPCR dimers, the interaction with receptor activity- modifying proteins, and the binding of PDZ domain-containing and non-PDZ domain scaffold proteins to intracellular receptor domains (Maudsley et al., 2005). Such interactions can modify GPCR pharmacology and trafficking, localize receptors to specific subcellular domains, limit signaling

to pre-determined pathways, and poise downstream effectors for efficient activation. Yet another modifier of GPCR signaling are small-molecule 'allosteric modulators' (Gesty-Palmer and Luttrell, 2011). When considered in the drug discovery context, allosteric modulators are synthetic molecules that change GPCR ligand affinity, efficacy, or both by binding the receptor at a site separate from the orthosteric ligand. Still, a number of endogenous compounds, including a variety of ions, lipids, amino acids, peptides, and physical stimuli display different degrees of receptor-specific modulatory effects (van der Westhuizen et al., 2015).

In this review, we discuss the involvement of one GPCR, the angiotensin II (AngII) AT1 receptor (AT1R), in peritoneal membrane fibrosis, a common complication of peritoneal dialysis (PD), and consider how ligand-dependent and ligand-independent AT1R signaling may contribute to its pathogenesis.

2. Peritoneal dialysis

2.1. Peritoneal membrane fibrosis

End-stage renal failure (ESRD) is an important health issue, with approximately 450,000 Americans on renal replacement therapy in 2012 (2014 United States Renal Data Systems). The annual cost of medical care for dialysis patients in this country exceeds $15 billion. Hemodialysis (HD) and PD are the current choices for dialysis, while patients wait for renal transplantation. PD is a unique biological situation, in that peritoneal mesothelial cells (PMC) in a single cell layer that lines the peritoneal mesothelium are exposed to elevated concentrations of glucose and glucose metabolites (e.g. advanced glycosylation end products) in the PD fluid, physical derangements (PMC shrinkage caused by hyperosmotic stress of the PD fluid and stretch of PMC caused by increased intraperitoneal volume), and acidic pH (5.5) of the PD fluid (for storage purposes). PD has distinct advantages (continuous nature, less hemodynamic instability, ability to dialyze at home, lack of needle sticks, increased ability to travel, patient independence) over HD. However, only about 10% of dialysis patients perform PD. Long-term PD is limited by the development of peritoneal fibrosis that begins soon after PD is initiated and progresses steadily. Disabling peritoneal membrane dysfunction eventually ensues, characterized by development of very rapid small molecule transport and ultrafiltration failure if marked angiogenesis accompanies the fibrosis or by development of failure to clear solutes. Fig. 1 depicts the morphological changes seen in the submesothelial layer of the peritoneal cavity after chronic PD. Many nephrologists are reluctant to utilize PD

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