Novartis – Unbranded RAAS Pathway Educational Video

OVERVIEW

This will be an unbranded KOL hosted video about 5-6 minutes in length. This will be a stand-alone piece that can live on tablet PCs for the sales force, on unbranded websites or as a part of unbranded platforms. The chief goal of this piece will be to create a greater understanding of the RAAS pathway and to illustrate its critical role in patients with hypertension, including those with comorbid diabetes.

CONTENT

Hello, my name is [KOL name], and I am here today to talk about the Renin Angiotensin Aldosterone System – or RAAS, as it is commonly called. Undoubtedly, you already know that the RAAS plays a key role in hypertension and are familiar with its basic pathway.[1] **[Jackson EK. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 11th ed. 2006: pg 789/col 1/P1/ln 1-2]** In this program we will focus on investigations and new insights about the renin and angiotensin II components of the pathway.

First, let's refresh with a quick overview. The RAAS maintains homeostatic arterial pressure by modulating both blood volume and vasoconstriction. [1] **[Jackson EK. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 11th ed. 2006: pg 789/col 2/P1/all]**
The initial step of renin release in the juxtaglomerular cells, or JG cells, in the renal glomerulus is a rate limiting step in the RAAS and is primarily regulated by four different factors. [1] **[Jackson EK. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 11th ed. 2006: pg 789/col 2/P3/ln3-5; 790, Fig 30-1; pg 791/col 1/P1/all and col 2/P3/ln 1-6]**

The three which stimulate renin release are: (1) Reduction in circulating blood volume, detected by the stretch receptors on JG cells; [1] **[Jackson EK. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 11th ed. 2006: pg 791/col col 2/P3/ln 1-6; pg792/Fig 30.2]** (2) Reduction in sodium chloride concentration registered by the macula densa cells near the JG cells, and; [1] **[Jackson EK. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 11th ed. 2006: pg 791/col 1/P1/all pg792/Fig 30.2]** (3) An increase in sympathetic activity via beta-1 adrenergic receptors. [1] **[Jackson EK. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 11th ed. 2006: pg 791/col 2/P4/all; pg792/Fig 30.2]** The fourth factor is angiotensin II– or Ang II. Renin production is inhibited by the direct action of Ang II on the JG cells in a negative feedback loop. [1] **[Jackson EK. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 11th ed. 2006: pg 790/Fig.1; pg 791/col2/P5/ln 2-5; pg792/Fig 30.2]**

Now, let's look downstream in the RAAS. Ang II is the primary active product of the pathway and via its effects on its receptor AT1, [1] it mediates blood pressure through the following mechanisms: **[Jackson EK. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 11th ed. 2006: pg 796/Fig. 30-3]**
(1) Vasoconstriction of renal and systemic arterioles; [1] **[Jackson EK. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 11th ed. 2006: pg 795/col2/P3/ln10-15;pg 796/col1/P1/all]** (2) Sodium resorption; [1] **[Jackson EK. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 11th ed. 2006: pg 797/col2/P4/all]** (3) Stimulation of aldosterone production in the adrenal cortex;[1] **[Jackson EK. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 11th ed. 2006: pg 797/col2/P5/all]** (4) Stimulation of the sympathetic nervous system;[1] (5) Inhibition

of renin release.[1] **[Jackson EK. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 11th ed. 2006: pg 790/Fig.1; pg 791/col2/P5/ln 2-5; pg792/Fig 30.2]**This last mechanism ties the beginning and the end of the path together and explains why if Ang II production is suppressed, there can be a resultant increase in renin production. **[Jackson EK. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 11th ed. 2006: pg 811/col1/P1/ln3-5]**

With the basics reviewed, let's consider the pathophysiology of hypertension. 7 out of 10 patients with untreated hypertension present with an overactive RAAS.[2] **[Alderman MH. Alderman *AmJHypertens.* 2004;17(1)pg2/col 1/P4/ln 2-5]** This figure includes those hypertensive patients with comorbid diabetes, whose ability to regulate RAAS is impaired compared to healthy subjects.[3] **[Price DA, Am J Hypertens. 1999;12(4): 352/col1/P2/ln 5-8; pg 348/col1/P1/ln24-30 and col2/P1/ln1-2]**

Let's take a closer look at renin and Ang II.

Preclinical animal data have shown that diabetic kidneys produce more renin than non-diabetic kidneys. Toma, et al., using in vitro animal models, showed that high glucose levels led to increased renin production'.
.[4] **[Toma et al, *J Clin Invest*. 2008;118(7) pg 2526/col2/p3/all - pg2527/col1/P1/all; col2/P1/all and Fig. 1;pg2530/col2/P2/ln1-5]** Looking here, you can see in green, the increased renin in the afferent arteriole in the JG cells of diabetic vs. nondiabetic mice.[4] **[Toma et al, *J Clin Invest*. 2008;118(7): pg2527 Fig. 1]**
Recall that the release of renin is the rate limiting step in the RAAS and leads to the production of angiotensin I, angiotensin II, and aldosterone'.
, this overproduction of renin may be a contributing factor to an overactive RAAS.[1] **[Jackson EK. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 11th ed. 2006: pg 791/col 1/P1/all]**

A clinical study by Price, et al. evaluated RAAS regulation in three cohorts – healthy controls, non-diabetic hypertensive patients and hypertensive patients with diabetes. Responsiveness was measured by plasma renin activity – or PRA.[3] **[Price DA, Am J Hypertens. 1999;12(4): 348/col2/P2/all;P5/ln1-3 –pg 350/col1/P1/ln1-3 and Table 1]** RAAS was activated by low sodium diet and tested while in a standing position. RAAS was suppressed by a high sodium diet and tested in a recumbent position.[3] **[Price DA, Am J Hypertens. 1999;12(4): 351/col1/P1/all; col2/P1-2/all and Table 2]** As you can see, healthy subjects were able to respond and suppress RAAS, but in hypertensive diabetic patients, RAAS activity was not as completely suppressed.[3] **[Price DA, Am J Hypertens. 1999;12(4): 351/col2/P2/ln 4-7 and Table 2]**

Turning to the end of the RAAS pathway, we will examine one study which demonstrated that blood pressure response to ang II is exaggerated in hypertensive patients, including those with diabetes.[5] **[Gordon M. *J RAAS.* 2000;1(3): 254/col2/P3/all]**

This study compared responsiveness of the RAAS in healthy subjects, nondiabetic hypertensive patients, and hypertensive patients with type 2 diabetes.[5] **[Gordon M. *J RAAS.* 2000;1(3): 252/col2/P3/ln1-10 and pg253/Table 1]** The subjects received a 45-minute infusion of Ang II - which would be expected to suppress RAAS activity, as measured by PRA.[5] **[Gordon M. *J RAAS.* 2000;1(3): 253/col1/P2/all]** Consistent with the previous study, healthy subjects and nondiabetic hypertensives suppressed their RAAS activity, with appropriate decreases in PRA.[5] **[Gordon M. *J***

***RAAS.* 2000;1(3): 253/col2/P4/all and Fig 1a]** However, the hypertensive diabetics did not experience significant RAAS suppression.[5] **[Gordon M. *J RAAS.* 2000;1(3): pg253/Fig.1a; pg 254/col1/P41/ln 2-11; P2/all]**

The data across these two studies suggests and Toma's animal models suggests that hypertensive patients with diabetes have an impaired ability to regulate RAAS activity compared with healthy subjects and hypertensive patients without diabetes.[3-5] As we have shown here, RAAS is an important target for treating hypertension, particularly in hypertensive patients with diabetes. **[Gordon M. *J RAAS.* 2000;1(3): pg253/Fig.1a; pg 254/col1/P41/ln 2-11; P2/all; col2/P3/all] [Price DA, Am J Hypertens. 1999;12(4): 351/col2/P2/ln 4-7 and Table 2] [Toma et al, *J Clin Invest.* 2008;118(7) pg 2526/col2/p3/all - pg2527/col1/P1/all; col2/P1/all and Fig. 1;pg2530/col2/P2/ln1-5]**

References:

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