ANGIOTENSIN II TYPE-1 RECEPTOR (AT1R) DISTRIBUTION IN BPH, HIGH GRADE PIN AND ADENOCARCINOMA OF THE PROSTATE

[1]Isdianto Septiadi, [1]Suwandi Sugandi, [1]Bambang S. Noegroho, [1]Tjahdjodjati, [1]Ferry Safriadi, [1]Safendra Siregar, [1]Ricky A, [1]Kuncoro Adi, [1]Aaron T. Sihombing, [1]Sawkar V. Pramod, [1]Ramlan Nasution, [2]Bethy S. Hernowo.

[1]Department of Urology, Faculty of Medicine/Padjadjaran University, Hasan Sadikin Hospital, Bandung.
[2]Department of Anatomical Pathology, Faculty of Medicine/Padjadjaran University, Hasan Sadikin Hospital, Bandung.

ABSTRACT

Objective: *The aim of the study was to detect the differences in number and distribution of angiotensin II type-1 receptor (AT1R) in BPH, high grade PIN, and adenocarcinoma of the prostate.* ***Material & method:*** *A prospective study was performed in RSHS, in collaboration with the Department of Anatomical Pathology. Prostate samples were taken by TUR of the prostate, and then divided into 5 groups. They were BPH, high grade PIN, adenocarcinoma of the prostate in 3 difference grades (well, moderate, and poorly differentiated). Kidney tissue served as control. Immunohistochemical staining was done to determine the angiotensin II type-1 (AT1R) receptor distribution as primary antibody mouse monoclonal antibody AT1 (TONI-1) was used.* ***Results:*** *Angiotensin II type-1 receptor was found in specimen from BPH, high grade PIN and adenocarcinoma of the prostate. The number and distribution of the receptors were not different.* ***Conclusion:*** *No significant differences in number and distribution of angiotensin II type-1 receptor on BPH, high grade PIN, and adenocarcinoma of the prostate were found.*

Keywords: *Angiotensin II, high grade PIN, adenocarcinoma of the prostate.*

Correspondence: Isdianto Septiadi, c/o: Department of Urology, Faculty of Medicine/Padjadjaran University, Hasan Sadikin Hospital. Jl. Pasteur No. 38 Bandung. Phone: 022-2039141.

INTRODUCTION

Prostate carcinogenesis is developing in a lengthy process and taking place through several steps due to genetic and epigenetic changes that result in balance alteration between cell proliferation, apoptosis, and differentiation. Normal prostate epithelium requires 10-30 years to develop into clinically detectable prostate cancer, and 10-20 years later into metastasis. Therefore, theoretically there is a chance to prevent prostatic malignancy with chemoprevention.[1] Angiotensin, particularly angiotensin II type-1 has cell proliferative effect (Diem T et al. 2001), in addition to the vasocontrictive effect.[2] The role of angiotensin in the development of prostatic cells has not be recognized. To find the role of angiotensin in prostate cells, the presence and distribution angiotensin II type-1 receptor (AT1R) in prostate tissue should be identified.

OBJECTIVE

To compare the distribution of angiotensin II type-1 receptor (AT1R) in BPH, high grade PIN, and prostate adenocarcinoma.

MATERIAL & METHOD

We studied the expression and compare the distribution of angiotensin II type-1 receptor (AT1R) in different types of pathology of the prostate, such as BPH, high grade PIN, and prostate adenocarcinoma immunohistochemically. The objects of study were 10 samples of BPH, 10 preparations of high grade PIN and 10 preparations of prostate adenocarcinoma. As primary antibody mouse monoclonal antibody AT1 (TONI-1): sc-57036, Santa Cruz Biotechnology, Inc., CA. was used.

RESULTS

From the immunohistochemical examination of all tissue samples, we found expression of the angiotensin II type-1 (AT1R) receptor in all prostate tissues (BPH, high grade PIN, and prostate adenocarcinoma). The receptor expression was in brown color. The distribution of angiotensin II type-1 receptor (AT1R) was found in the stroma cells of prostatic tissue in all preparations with equal intensity. There was no expression in epithelium cells.

Table 1. The expression of angiotensin II type-1 (AT1R).

Types of tissue	Expression of angiotensin II type-1 Receptor (AT1R)		
	Epithelium	Stroma presence	Stroma intensity
BPH	-	+	++
High grade PIN	-	+	++
AdenoCa	-	+	++

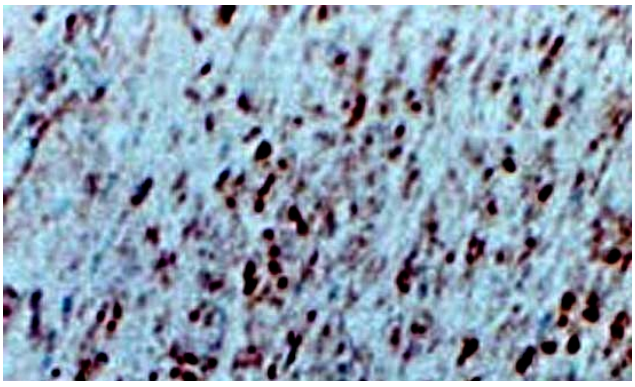

Figure 1. The expression of angiotensin II type-1 (AT1R) in BPH.

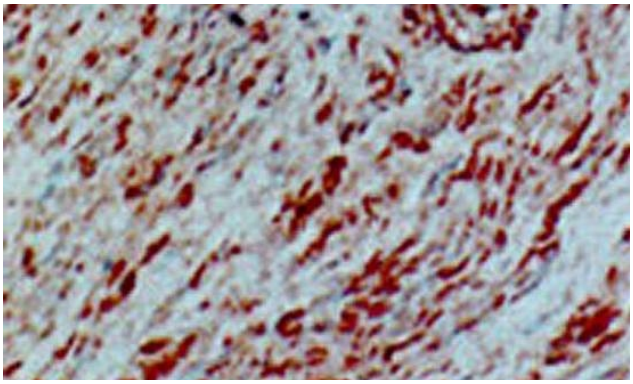

Figure 2. The expression of angiotensin II type-1 (AT1R) in high grade PIN.

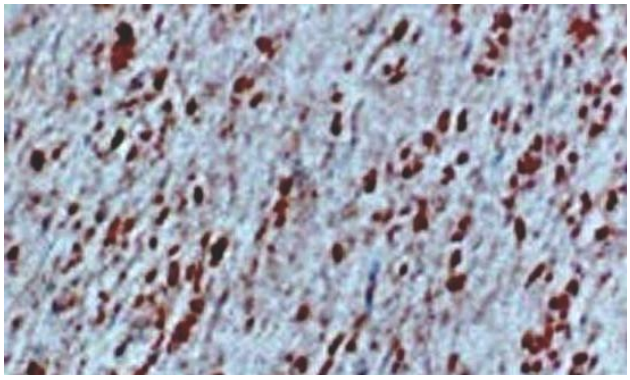

Figure 3. The expression of angiotensin II type-1 (AT1R) in prostate adenocarcinoma.

DISCUSSION

In vitro studies revealed that angiotensin II receptor in human prostate tissue is predominated by the AT1 subtype and mostly present in the periurethral area. Immunohistochemistry showed the AT1 receptor was located in the cells of muscular stroma. In several tissues, angiotensin II was found to increase the tonus of smooth muscles,[3] and to stimulate cell proliferation and growth.[2,4] It is very likely that angiotensin II enhances also cellular growth and increases symphatic tonus in the prostate. Both are the factors that play role in the pathophysiology of BPH.[5,6] It has been shown that angiotensin II facilitates symphatetic transmission,[7] by enhancing the release of the noradrenalin neurotransmitter from a symphatetic nerver terminal.

Angiotensin II has a mitogenic effect on various cells, such as blood vessel smooth muscle cells, hepatic stellate cells, fibroblasts, hematopoietic progenitor cells, and mesothelial cells. There are two types of angiotensin II receptor that play here a role, i.e., angiotensin 1 (AT1) receptor and angiotensin-2 (AT2) receptor. The mitogenic effect and blood pressure regulation is regulated by AT1 receptor. Latin et al. (2000) found that malignancy in the prostate is mediated by angiogenesis, which in this case is caused by the vascular endothelial growth factor (VEGF).[1] The increase of VEGF correlates with clinical aggressiveness. Angiotensin II also plays a role in cytokine secretion, and the cytokine is involved in angiogenesis. Blockade to angiotensin II specific receptor may inhibit VEGF production, leading to the inhibition of the angiogenetic process.[8-12]

In this study, we performed immunohistochemical examination to observe AT1 receptor in prostate tissue and its distribution, with the finding that there was angiotensin II type-1 receptor in the preparations of BPH, high grade PIN, and prostate adenocarcinoma. The number and distribution of angiotensin II type-1 in the preparations of BPH, high grade PIN, and prostate adenocarcinoma were not different. This was likely because the sample was taken from the periurethral zone with a TURP, while prostate adenocarcinoma occurs most frequently in peripheral zone. Studies using an intact prostate sample such as from radical prostatectomy operation are needed to observe AT1 receptor distribution in the required prostate zone.

CONCLUSION

Angiotensin II type-1 receptor is present in the preparations of BPH, high grade PIN, and prostate adenocarcinoma. The number and distribution of angiotensin II type-1 receptor in those preparations are the same in all tissues.

REFERENCES

1. Klein E, Platz E, Thompson I. Epidemiology, etiology, and prevention of prostate cancer. Campbell Walsh Urology. 9th ed. 2007; 90: 2866-7.
2. Diem T, Albert G, Melissa Sourial. Identification, distribution, and expression of angiotensin II receptors in the normal human prostate. Endocrinology 2001; 142: 1349-56.
3. Brunner HR, Nussberger J, Waeber B. Tissue angiotensin generation and regulation. Pharmacol Ther 2001; 65: 193-213.
4. Matsubara H, Inada M. Molecular insights into angiotensin II type 1 and type 2 receptors: Expression, signalling and physiologic function and clinical application. Endocrinology J 1998; 45: 137-50.
5. Csikos T, Chung O, Unger T. Receptors and their classification: Focus on angiotensin II and the AT2 receptor. J Hum Hypertens 1998; 12: 311-8.
6. Maruenda J, Bhatnagar V, Lowenthal DT. Hypertension in the elderly with coexisting benign prostatic hyperplasia. Urologie 1999; 53: 7-12
7. Story DF, Ziogas J. Interaction of angiotensin II with noradrenergic transmission. Trends Pharmacol Sci 1987; 8: 269-71
8. Hiroji U, Hitoshi I, Yoji N, Takeshi S. Antiproliferative activity of angiotensin II receptor blocker. Molecular Cancer Ther 2005; 4: 1699-709.
9. Huckle WR, Earp HS. Regulation of cell proliferation and growth by angiotensin II. Prog Growth Factor Res 1994; 5: 177-94.
10. Harrison-Bernard LM, Navar LG, Ho MM. Immunohistochemical localization of Ang II AT1 receptor in adult rat kidney using monoclonal antibody. Am J Physiology 1998; 273: 170-7.
11. Van Sande ME, Scharpe, Neels HM. Distribution of angiotensin converting enzyme in human tissue. Clin Chim Acta 1995; 147: 255-60.
12. Yokoyama M, Takaha M, Iwata H. Angiotensin-converting enxyme in the human prostate. Clin Chim Acta 1980; 100: 253-8.