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# Angiotensin receptors: their pharmacological aspects and side effects vis-à-vis receptor blocker drugs

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**ABSTRACT**

Receptors are the protein molecules embedded in plasma membrane, cytoplasm or nucleus. Receptors received its chemical signals originating from the cells. Through binding to receptors these signals directed cell to produce its action. There are different psychological actions produced by Angiotensin-II such as increase in extracellular volume, peripheral vascular resistance and blood pressure. It is also involved in regulation of cell growth and differentiation. Angiotensin-II Receptor is of two types, AT-I and AT-II. Most of the functions of angiotensin-II are regulated by AT-I. Physiological role of AT-II are not known. Various vital organs of the body like Heart, lungs, kidney, adrenal cortex and brain are rich in AT-I Receptor. Those drugs which block the action of AT-1 on blood vessels and Heart are called as Angiotensin Receptor Blocker (ARBs). There are different ARBs available in the market which are well tolerated and having fewer side effects. ARBs biding affinity towards the receptors is like as condensatran > ibesartan> valsartan> telmisartan> tasosartan> losartan >eprosartan. The main severe side effect shows by ARBs is swelling of tissues, liver and kidney failure, allergic reactions.

**Keywords**: Membrane, cytoplasm, psychological.

All physiological actions of angiotensin-II in cardiovascular, hepatic renal, endocrine and other target cells are shown by Angiotensin AT-1 receptor. All these activity responsible for regulation of different body function like hormone secretions, arterial blood pressure, electrolyte and water balance, thirst, and renal function. AT-1 receptor is from G-Protein Coupled receptor family .After binding to the AT-1 receptor, Angiotensin-II shows its physiological reactions (De Gasparo *et al*., 2000). There are different cellular response of AT-1 receptor including smooth muscles contraction, proliferation, aldosterone secreation, neurosecreation, ion transport, steriodogenesis, and cell growth. The $AT_1$ receptor is coupled with well

**Table 1.** Pharmacokinetic aspects of angiotensin receptor blockers, active metabolites and their therapeutic effects

| Drug | Active Metab. | Bioav. (%) | Food Effect | Half Life | (Hrs.) | Protein | Binding | Route of Eli. | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | DRUG | Metab. | Drug | Meta. | Renal | Hepatic |
| Losartan | YES | 33 | NO | 2 | 6-9 | 98.7 | 99.8 | 35 | 60 |
| Valsartan | NO | 25 | YES | 9 | - | 95 | - | 13 | 83 |
| Irbesartan | NO | 70 | NO | 11-15 | - | 90-95 | - | 20 | 80 |
| Candesartan | YES | 42 | NO | 3.5-4 | 3-11 | 99.5 | - | 33 | 67 |
| Telmisartan | NO | 43 | NO | 24 | - | >99 | - | 0.5 | >97 |
| Epros Artan | NO | 15 | NO | 5-7 | - | 98 | - | 7 | 90 |
| Olmesartan | YES | 26 | NO | 13 | - | >99 | - | 35-50 | 50-65 |

defined $G_q$-mediated calcium and protein kinase C signaling pathways as well as intracellular signaling cascade till to the nucleus. These different pathways are responsible for the regulation of gene transcription and the expression of proteins which control the growth responses and proliferation of cell in Angiotensin-II target tissues. Some of the later consequences of $AT_1$ receptor activation are counteracted by the structurally dissimilar $AT_2$receptor, which antagonizes the effects of $AT_1$-mediated growth responses in several cell types, in particular endothelial cells, cardiomyocytes, and ovarian granulosa cells. This account of the $AT_1$ receptor will address its gene expression, ligand binding, activation and signal transduction pathways, and physiological roles in the regulation of the activity and growth of its major target cells in cardiovascular, neuronal, and endocrine tissues.

Angiotensin-II receptor blockers are the new class of drugs which classified under antihypertensive agents drugs .ARBs mode of action is different from other Angiotensin converting enzyme (ACE) inhibitors. ACE also works on Renin Angiotensin System. Because of binding to the receptor site, ARBs produces the complete inhibition of Angiotensin-II action. A lot of ARB drugs are available in the market. which are approved by Food and Drug Administration for the treatment of hypertension, for the use either alone or in combination with other drugs (SPI, 2002; Olin, 2002). The different drugs available in the market are condensartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan and valsartan.

Those drugs which are used for the lowering blood pressure can cause some side effects like dizziness, headache, cold flu and others. Kidney failure, liver failure and some allergic reactions like swelling around the mouth and throat are also shows by these drugs but rarely. (Rodgers and Patterson, 2001).

Different Angiotensin-II receptor blocker shows same mode of action but all of them has different efficacy and pharmacokinetic profile with low side effects. ACE inhibitors affect the bradykinin level of body but ARBs do not affect bradykinin level but they are contraindicated in pregnancy.

**Pharmacology of Angiotensin Receptor Blocker**

Pharmacology of ARBs depends on the Rennin Angiotensin Systen (RAS). In RAS renin converts the angiotensinogen to an inactive decapeptide Angiotensin-I (Dzau *et al.*, 1993; Urata *et al.*, 1990; Linz *et al.*, 1995). Then After angiotensin-I is converted to angiotensin-II by Angiotensin converting enzyme. Angiotensin-II is the main end product of this cycle. Different type of pathogenesis reactions like essential Hypertension, reno-vascular hypertension, congestive heart failure and renal disease associated with albuminuria are produced by angiotensin-II. Because of ACE inhibitors, when rennin angiotensin system blocks its shows few side effects also like cough, and angioedema (Burnier and Brunner, 2000; Bumier, 2001; Rodgers and Patterson, 2001).

Angiotensin Receptor Blocker work by inhibition of Angiotensin-II by competitive blocking the angiotensin-I receptor and it reduce adverse effect and possibly improve clinical efficacy.

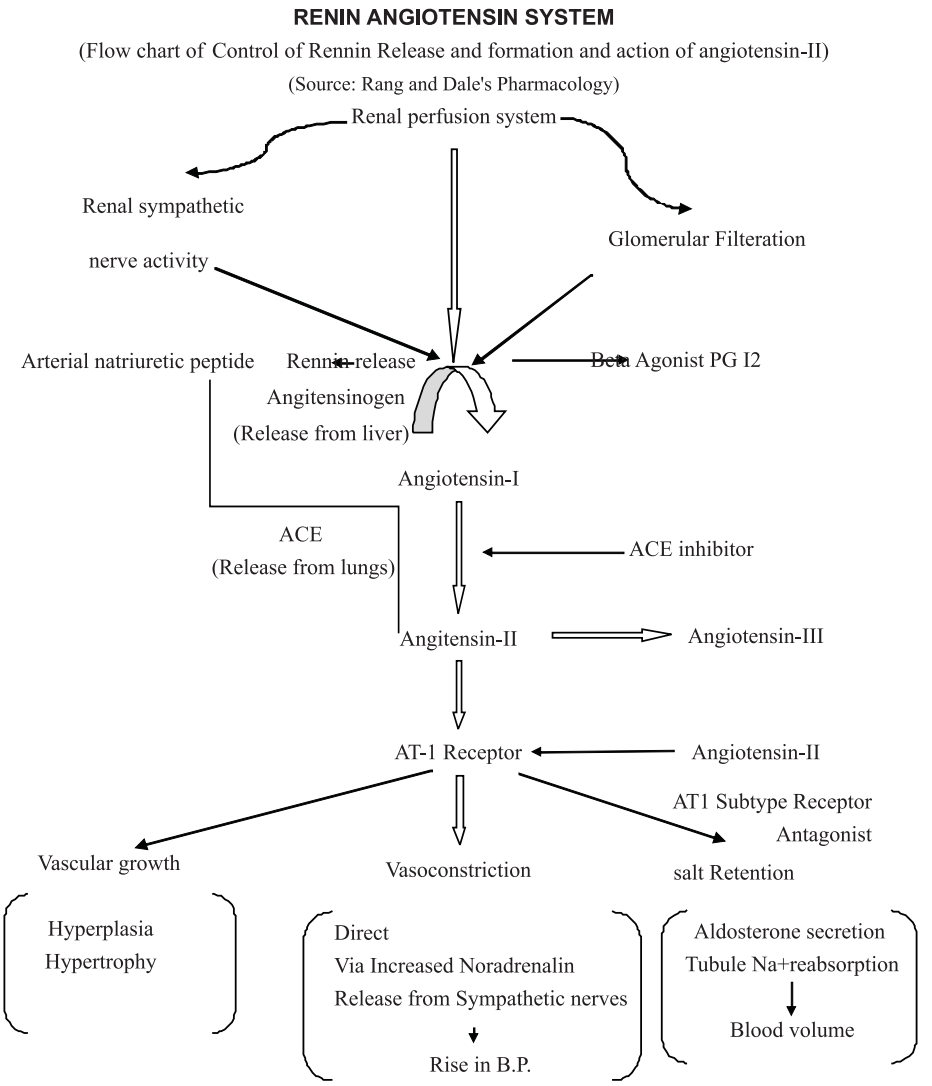


**Figure 1**

Blood vessels narrows because of entry of Angiotensin-II in to the blood stream which leads to increase of blood pressure of the body. It also activates a hormone which causes the water retention of body. ARBs having a very high affinity towards the AT-1 Receptor but negligible affinity towards AT-2 receptor.

When AT-I receptor blocks by ARBs it leads to lowering of blood pressure because of Antagonizing angiotensin-II. Which further induced vasoconstriction, aldosterone release, catecholamine, arginine, vasopressin release, water intake, and hypertrophic response and other reactions?

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**Figure -2 Physiological Regulations of Electrilyte Balance, Plasma Volume and Blood Pressure by the Renin Angiotensin System**

(*Source* -Essential of Medical Pharmacology by K.D.Tripathi)

**Different available ARBs and their side effects-**

ARBs include following drugs-

- Condensartan
- Eprosartan
- Irbesartan
- Losartan
- Olmesartan
- Telmisartan
- Valsartan

ARBs are the first choice for treatment for most people who having blood pressure. Because they are well tolerated with less side effect in comparison to ACE inhibitors because they do not affects bradykinin level of body. But ARBs are recommended to people those people who are less then 55yrs of age. But contraindicate in women who are pregnant, breastfeeding or planning a pregnancy.

The most common side effects of ARBs are like dizziness, headache, cold or flu etc. The side effects of cough found less in patient treated with ARBs as comparison to patients treated with ACE inhibitors. And the rare side effects are like swelling of lips, tongue or face .Some time ARBs causes increase in Potassium level of body and changes in kidney function.

**Condensartan**

Condensartan is prolonging effective angiotensin-II receptor antagonist with best angiotensin-II antagonist activity. AT-1 binding affinity in rabbit aorta is 80 times greater than losartan. Elimination takes place through Kidney (Approx.60%) and Bile (Approx.40%).General side effects of condensartan are runny or stuffy nose,

sore throat, cough, back pain, joint pain, stomach pain, diarrhea, headache, and dizziness. And others side effects of condensartan like chest pain, swelling in hands or feet, slow heart rate, weak pulse rate and tingly feeling are serious to take.

**Eprosartan**

Eprosartan is categorized in latest angiotensin-II receptor antagonist. Half life of Eprosartan is short and absorption is reduces if taken with food. Metabolism of Eprosartan takes place in liver and converted in to glucuronide and then excreted through urine. Acute liver injury caused by ARBs and taking of alcohol can have an additive effect. They can rarely cause skeletal muscle breakdown which aggravated the kidney failure.

**Ibesartan**

Ibesartan is long effective AT-1 receptor antagonist as compare to losartan and valsartan. It is having high binding affinity towards the AT-1 receptor but shows no affinity towards AT-2 receptors. It is eliminated through kidney and bile. Generally reported side effects is gastrointestinal side effects like diarrhea ,dyspepsia ,abdominal pain, nausea, vomiting, and constipation, fatigue, headache, chest pain muscles weakness sexual dysfunction, alteration in libido. Allergic reactions reported very rarely by Ibesartan.

**Losartan**

The first oral active AT-1 receptor blocker is Losartan. It shows negative side effects in to the body. Flu, cramping of muscle, back pain, stomach pain, diarrhea and insomnia are mild side effects. Cramping of muscle, back pain and weakness in combination with fever, vomiting, dark color of urine are dangerous side effects of Losartan.

**Olmesartan**

Olmesartan is a specified angiotensin-II type 1 antagonist which can be use alone as well as in Combination with other antihypertensive drugs. Its bioavailability is unaffected by food. Dizziness is a common side effect of it but skin rashes, itching, swelling oh head or neck, difficulty in breathing or swallowing and decreased amount of urine produced are serious side effects produced by Olmesartan

**Telmisartan**

It is the long acting angiotensin-II receptor antagonist. Excretion takes place through feces(98%).Upper respiratory tract infection, back pain, inflammation of

sinuses, dry mouth, migraine and gout are the common side effects reported and skin rashes, swelling of head or neck reported are serious side effects.

**Valsartan**

It is a potent angiotensin-I antagonist, which is excreted by kidney and bile. Its absorption decreased (approx 40%) by food. Most common side effects are like fatigue, stomach pain, Infection with cold, flu, hair loss, dizziness, cough and anxiety but difficulty in breathing or swallowing and decrease amount of urine output are serious conditions.

**Future Development**

In the treatment of different disease related to cardiac activity like hypertension, congestive heart Failure and renal disease, angiotensin receptor blockers combinations and ACE inhibitors are mostly preferred to block the Rennin Angiotensin System. Combination of these drugs can improve blockade of Rennin Angiotensin System (*Azizi M et. al., 1995*).There are a lot of studies done to assess the effect of combination of drugs and their side effects elated to treatments. Some contradictory result is available on the subject of the dosing of AT-1 receptor and ACE inhibitors.

**Conclusion**

Today disease related to cardiac problem is major issue for medical practitioners. There is a lot of studies are present for different angiotensin receptor blockers .Different studies shows that ARBs drugs are equally effective like ACE inhibitors, beta blockers, calcium channel blocker in the treatment of mild to moderate hypertensive patients. ARBs are reported with lesser side effects as compare to other class of drugs. And they are well tolerated also. ARBs show strong activity in the management of Hypertension, Heart failure, or Renal disease. Rarely patients are reported with major side effects Damage of organ and reduced cardiovascular morbidity and mortality prevented by ARBs.

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