Emergence of extracellular domain-functions of GPCRs: Appreciating Gobind's vision

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More than 25 years ago Gobind predicted that elucidating extracellular domain functions in Gprotein-coupled receptors (GPCRs) would open up new opportunities. Recent advances in solving crystallographic structures and analysis of dynamic functions of GPCRs establish Gobind's vision. In many instances including angiotensin receptors, mechanism of GPCR-mediated autoimmunity and intervention for the conditions with therapeutic drugs is based on the extracellular domain. In this presentation, determination of 3D-structure of the angiotensin receptor, auto-immune disease based on the extracellular domain and development of drugs targeting the extracellular domain will be discussed. The Angiotensin II type 1 receptor (AT1R) is a 359 residue long rhodopsin-like GPCR that selectively binds lifesaving antihypertensive drugs, clinically referred to as ARBs. In humans AT1R is the principal mediator of functions of the rennin angiotensin system (RAS) that include regulation of cardiac, vascular and renal hypertrophy, matrix remodeling and inflammation. Retrospective studies in humans provide evidence that long-term use of these drugs indeed protect against cardiac, vascular and renal hypertrophy, aortic aneurism, fibrosis, breast tumor growth and inflammation. Autoimmune antibodies targeting epitopes in the extracellular loops of AT1R cause diseases such as preeclampsia and malignant hypertension which cannot be treated with currently available ARBs. Based of the crystal structure and molecular dynamics simulation studies we have developed chemical inhibitors that prevent antibody binding to AT1R.