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OPTICALLY ACTIVE ANGIOTENSIN RECEPTORS

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Optogenetics is a relatively new field that allows us to better understand receptor signaling by creating chimeric receptors that can be activated by light. Along these lines, we have created optically active versions of angiotensin 1 and 2 receptors (AGTR1/2), by combining the native G protein-coupled receptors (GPCR) with portions of the light-sensitive rhodopsin GPCR, with the hope that this will help elucidate the role of the angiotensin pathway in preeclampsia. Our goal was to determine which amino acid substitutions are necessary and sufficient for the ligand active AGTR1/2 to become optically active (oAGTR1/2) as well as functionally equivalent. We characterized the chimeric receptors through western blot and internalization assays to confirm a functioning GPCR through the G protein and arrestin pathways. Measurement of phosphorylated ERK (p-ERK) levels was done at five different time points in western blots by transfecting HEK cells with oAGTR1/2-GFP. We confirmed that white light confers G protein activation through the MAPK/ERK pathway and achieves the same biphasic levels as its cognate ligand active receptor. We also utilized confocal microscopy to visualize the internalization of the novel GPCR's by arrestin and compared it to the native receptors using the same HEK cells. We confirmed that arrestin dependent internalization of the optically active receptor is achieved by 30 minutes after dosage of white light and parallels the response of its ligand activated native receptor. The assays performed support our hypothesis that the ligand activated AGTR1/2 could be modified to become optically active by changing only a few key amino acids (A/F113E and Y/F296L). The next key step is to characterize the chimeric receptors *in vivo* using Cre recombinase-dependent adeno associated viruses in order to further confirm functional equivalency of the optically active receptors.