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Cell Surface Binding, Intracellular cAMP Elevation and Membrane Associated G-Protein Activation by (R,R)– and (S,S)–Formoterols in Androgen Independent Human Prostate Cancer Cell Line, PC3

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Abstract —The commercially available long acting anti-asthmatic drug, formoterol exists as a racemate of four enantiomers ((R,R)-, (R,S)-, (S,R)- and (S,S)-. The study describes several comparisons between two completely different enantiomers, (R,R)- and (S,S)- based on their # 1) cell surface binding, # 2) cAMP elevation ability, # 3) G-protein activation and # 4) inhibition of DNA synthesis in PC3 cells. The presence of high affinity □2-adrenergic receptor (Kd ~ 30 pmol/L) was confirmed by competition binding of 125I-cyanopindolol with increasing concentration of (R,R)-formoterol using both intact PC3 cells and isolated plasma membrane. Replacing (R,R)- by (S,S)- yielded no significant binding interaction proving its ineffectiveness toward the □2-adreno-receptor. While both were capable of eliciting prolonged cAMP generating activity in intact PC3 cells, the EC50 values (R,R- = 10.5 pM, R,S- = 11.0 pM and S,S = 1000 pM) varied nearly 100 fold in favor of (R,R)- and (R,S)-. Propanolol effectively inhibited cAMP elevation in intact cells in both the cases as also agonist stimulated incorporation of [□32P]-GTP-AA (Guanosine triphosphate azidoanilide) by (R,R)- in isolated PC3 membrane, but failed in both events in the presence of (S,S)- enantiomer although incorporation of [□32P]-GTP-AA is specific for both the enantiomers. The unique discriminatory behavior is further observed in presence of muscarinic agonist, carbachol, which potentiated cAMP generation by (R,R)- nearly 2–3 fold, but was unable to do so in the presence of (S,S)-. These facts confirmatively indicate that cAMP elevation by (S,S)- in PC3 cells occurs entirely via a different pathway than its (R,R)-counterpart. Interestingly, both enantiomers can effectively lower the DNA synthesis, showing superior efficacy of (R,R)-.

Keywords : *Binding, □2-Adrenergic Agonist, Androgen, Formoterol, Prostate Cancer, PC3, LnCaP, Du145, G-Protein, □-Adrenergic Receptor, Enantiomer.*