

The Glutamic-384 and Glutamine-384 Variant of the Beta 1 Adrenergic Receptor Exhibit Constitutive Activity and Differentiate Coupling of G-protein

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The Beta 1 adrenergic receptor is a major mediator of catecholamine effects in the human heart. It is the principal subtype of Beta adrenergic receptors regulating human heart rate and contractility. Stimulation of the Beta 1 adrenergic receptor by catecholamines results in the activation of the heterotrimeric G-protein, which, in turn, activates the enzyme, adenylyl cyclase, and promotes the production of cyclic AMP. Increased production of cyclic AMP provides a greater risk of heart failure due to increase in heart rate and contractility. Blockade of the Beta 1 adrenergic receptor has proved to be effective in the treatment of chronic heart failure. Mutating the receptor, through site directed mutagenesis, allows a better understanding of variant receptor activity. Two variants of the beta receptor were tested in this experiment and were compared to the wild type receptor by measuring the accumulation of the second messenger, cyclic AMP. Compared to the wild type receptor which has arginine at the 384 position, both types of variants, the glutamic acid and glutamine receptors, both demonstrated characteristic features of constitutively active receptors. Both variant types increased adenylyl cyclase enzyme activity compared to the wild type receptor. The glutamic acid variant showed similar amounts of cyclic AMP as did the wild type prior to receptor stimulation. The glutamine variant showed a much higher increase in enzyme activation compared to the wild type. In addition, adenylyl cyclase activity had increased prior to the addition of agonist. Mutating the beta adrenergic receptor with the respective variants suggests that arginine at the receptor 384 position holds a prominent role in receptor-G protein interactions. By mutating the wild type receptor at the 384 position from a basic residue to an acidic or neutral residue of similar mass results in an increase of downstream signaling events.