

## Structural analysis and molecular modeling of Human dopamine receptor 5 (DRD5)

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**Abstract-** Dopamine has been shown to play a key role in the Central Nervous System. Any imbalance in dopamine production and dopamine receptor activity has been implicated widely in the pharmacology, of a number of neurobehavioral disorders existing today. The dopamine receptors interact with G-proteins to transduce dopamine stimulation into intracellular responses. In this work a 3D structure of DRD5 based on the template of High resolution crystal structure of human  $\alpha$ -2 adrenergic receptor (PDB code 2RH1A) was generated. The model was assessed using MOLPROBITY. The results revealed that 94% of the residues were found in the favoured region of Ramachandran's plot. Active site analysis showed that predicted binding sites included all the seven transmembrane helices. Our work demonstrates that in silico modeling of proteins has been shown to play an important role in determining protein structure and provides a promising area in possible drug discovery.

### Introduction

#### Parkinson disease and Dopaminergic receptor

Parkinson's disease (PD) is a neurodegenerative disease which affects large number of people worldwide. The symptom of Parkinson's disease (PD) comprises conditions of motor system disorders resulting in tremor, stiffness of limbs and trunk; bradykinesia, and postural instability [1](Civelli *et al.*, 1993). Evidence suggests that these conditions, are due to loss of dopamine-producing brain cells caused by degeneration of dopaminergic neurons in the substantia nigra of the mid brain region and other monoaminergic neurons in the brain stem (Forno., *et al* 1996).

Dopamine has been shown to play a key role in the central nervous system, contributing to important functions of attention, movement of different parts, perception, motivation and emotion. Imbalance in dopamine production and dopamine receptor activity has been implicated widely in the pharmacology, of a number of neurobehavioral disorders existing today (Zhang *et al.*, 2006).

Elaborate understanding of dopaminergic receptor has revealed that they follow three neuronal pathways viz the nigrostriatal pathway, mesocorticolimbic pathway and the tuberoinfundibular pathway. Of the three pathways, degeneration of nigrostriatal pathway which comprises of the neurons of the substantia nigra, and synthesizes dopamine that responds to it leads to Parkinson's disease (Civelli *et al.*, 1993).

#### Dopaminergic signaling

Dopamine an important neurotransmitter plays critical role in transmission of stimuli.

Dopaminergic signaling in brain has been shown to be mediated by five receptor subtypes through a cascade of intermolecular reactions and can be organized into D1-like (D1 and D5) and D2-like (D2, D3, and D4) classes based on pharmacological and physiological evidences (Missale *et al.*, 1998). The dopamine receptors interact with G-proteins to transduce dopamine stimulation into intracellular responses. The relative homology of D1 and D5 receptors suggests that receptors of the same subfamily might couple to the same set of G proteins for signal transduction. This observation has been shown for D1 like receptors where these receptors interact with Gs complexes resulting in the activation of adenylyl cyclase increasing the intracellular CAMP levels whereas the D2 receptor interacts with Gi complexes to inhibit CAMP production. These biological activities placed the two dopamine receptors in the super family of G protein-coupled receptors (Civelli *et al.*, 1993).

#### G-Protein coupled Receptors

GPCR form the largest group of membrane receptors having seven trans membrane  $\alpha$  helices which share similar sequence stretches of about 25-35 consecutive residues. Crucial to the mechanism of the receptors they must be able to interact with G-Protein to mediate signal transduction in response to extra cellular stimuli. Current estimation shows that almost 50% of the modern drugs sold throughout the world are targeted to these receptors (Wolf *et al.*, 2008, Chelikani *et al.*, 2004).

GPCRs super family comprises of five structurally distinct families which include the Rhodopsin like