Artery Research (2017) 19, 29–37

Available online at www.sciencedirect.com

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journal homepage: www.elsevier.com/locate/artres

Interaction studies on catecholamines to cellular receptors using *in silico* approach

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Received 26 January 2017; received in revised form 29 March 2017; accepted 6 June 2017

KEYWORDS
Catecholamines;
Dopamine;
Epinephrine;
Neurotransmitters;
Isoproterenol and nor-epinephrine

Abstract Catecholamines are organic compounds derived from amino acids tyrosine and phenylalanine, which acts as neurotransmitters and also functions as hormones in the blood circulation. They bind to plasma proteins and circulate in the blood stream. High levels of catecholamines will cause increase in the heart rate, blood pressure and blood glucose level. These effects are due to binding of catecholamines with adrenergic receptors. Therefore the objective of the current research work is to know the binding affinity of catecholamines with adrenergic receptors through *in silico* approach. For this study, four catecholamines and three adrenergic receptors were selected for binding analysis. The three natural catecholamines are epinephrine, nor-epinephrine, dopamine and a synthetic catecholamine is Isoproterenol. The three selected receptors are 1GQ4, 3D4S and 1BAK. Binding effect of the four neurotransmitters with the three receptors was studied through *in silico* analysis using softwares. PATCH DOCK and Z DOCK online servers were used to analyze the docking scores and internal energy was observed by Accelrys Discovery studio. From this study the synthetic catecholamine Isoproterenol showed maximum binding score with all three adrenergic receptors comparing to 3 natural catecholamines. The internal energy of Isoproterenol was found to be 35.18127 kJ/mol. Therefore the study concludes the synthetic catecholamine Isoproterenol has more binding affinity towards beta adrenergic receptors comparing to natural catecholamines. Hence, the current study suggests the usage of synthetic catecholamines will have more binding affinity with adrenergic receptors which could be further analyzed using *in vivo* study as a future work.

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http://dx.doi.org/10.1016/j.artres.2017.06.001

Background

Catecholamine is a group of amines (nitrogen-contain organic compounds) derived from the amino acid tyrosine and containing a catechol group (aromatic chemical compound consisting of a benzene ring with two hydroxyl groups). Catecholamines are important as neurotransmitters and hormones. They are classified into two major types, natural and synthetic catecholamines. Natural catecholamines are classified into three types they are epinephrine (adrenaline), Norepinephrine (nor adrenaline) and Dopamine. Synthetic catecholamine derivative of epinephrine. The most abundant catecholamines are epinephrine (adrenaline), norepinephrine (noradrenaline) and dopamine, all of which are produced by phenylalanine and tyrosine. Catecholamines as hormone are released by the adrenal glands in situations of stress such as psychological stress or low blood sugar levels.[1] The synthesis, function, and degradation of catecholamines reflects the complexity and harmonious coordination in bodily systems. Their synthesis and degradation involve a series of enzymatic steps, and as hormones the catecholamine's epinephrine, norepinehprine, and dopamine are produced in one part of the body to impact cells in other parts. Various disorders result when this complex coordination is disrupted.

Catechol or pyrocatechol is a benzenediol (aromatic chemical compounds in which two hydroxyl groups are substituted onto a benzene ring) with the formula $C_6H_4(OH)_2$. An amine group is a functional group that contains nitrogen as the key atom. Thus, a catecolamine has the distinct structure of a benzene ring with two hydroxyl groups, an intermediate ethyl chain, and a terminal amine group. Some of them are biogenic amines (substances produced by life processes). Catechols can form stable complexes with various di- and trivalent metal ions, the complexes with trivalent ions being the most stable. Catechols can also undergo redox reactions, cycling between catechols, semiquinone radicals and *ortho*-benzoquinone. The acidity dissociation constants (pK_a) for catechol at pH 7: pK_{a1} — 9.25[2]; pK_{a2} — 13.0.[3] The acidity dissociation constant for the catechol radical can, however, be much lower. The pK_{a1} of the hydroquinone radical as pH 4.1, and pH 9.85 for hydroquinone.[4] Thus, catechol occurs in the non-dissociated form and the catechol radical most probably in the dissociated form at physiological pH. The partitioning coefficients of catechol in an *n*-octanol water system (K_{ow}) and in a membrane-water system (K_{mw}) are 7.85 and 4.47 respectively.[5] Catechol is not very lipophilic and does not accumulate considerably in membranes or fatty tissues.[6] Alkylated or halogenated catechols, however, have higher partitioning coefficients and will therefore accumulate in lipids.

Catecholamines have several functions in the biological system, they help the body respond to stress.[7] Catecholamines are water soluble and are 50% bound to plasma proteins, so they circulate in the bloodstream. Two catecholamines, norepinephrine and dopamine, act as neuromodulators in the central nervous system and as hormones in the blood circulation. The catecholamine norepinephrine is a neuromodulator of the peripheral sympathetic nervous system but is also present in the blood (mostly through "spillover" from the synapses of the sympathetic system).[8] These hormones cause dilation of the pupils, increase the speed of nerve impulse transmission, widen small air passages in the lungs, and provide additional energy for the body. Norepinephrine causes an increase in blood pressure and epinephrine causes the body's heart rate to increase.

G protein coupled receptors (GPCRs), also known as seven-transmembrane domain receptors, 7TM receptors, heptahelical receptors,[9] serpentine receptor, and G protein-linked receptors (GPLR), constitute a large protein family of receptors that sense molecules outside the cell and activate inside signal transduction pathways and, ultimately, cellular responses.[10] The adrenergic receptors are a class of G protein-coupled receptors that are targets of the catecholamines, many cells possess these receptors, and the binding of a catecholamine to the receptor will generally stimulate the sympathetic nervous system.[11] The sympathetic nervous system is responsible for the fight-or-flight response, which includes widening the pupils of the eye, mobilizing energy, and diverting blood flow from non-essential organs to skeletal muscle.[12]

The major focus of this research work done is to identify the binding sites of adrenergic receptors and compare the binding efficiency of different types of catecholamines with adrenergic receptors. This includes the selection of catecholamine compounds, analysis of binding sites of human adrenergic receptor with catecholamines (by *in silico* studies through discovery studio software)[13]; to find the compound that shows the best docking score, to check binding pockets and cavities using CASTp and to check for competitive binding using patch dock. The specific reason to choose the adrenergic receptors is mainly to know the exact mechanism of interaction of Isoproternaol (ISPH) compound that has been used in several clinical research studies as a drug to induce experimental myocardial infarction (MI) in experimental animals. Therefore the current study has chosen the adrenergic receptor to know the interaction studies of catecholamines in cellular receptors.

Materials and methods

The binding of ligand molecules (catecholamine), with its respective receptors (Adrenergic receptors) is studied by obtaining the ligand molecules using the PRODRG server and ACCELRYS DISCOVERY STUDIO software. Similar methods were used to obtain Human receptor molecules. Then the docking of receptor and ligand molecules was done using DS LIGANDFIT and DS LIGANDSCORE. The structure of receptor molecules were obtained from protein databases such as RSCB and NCBI. Then the catecholamine compounds were isolated and docked using PRODRG server. Finally, the docking of adrenergic receptors and the catecholamine ligand molecules was done through PACTH dock studies and the results were analysed.

Steps involved in obtaining catecholamine ligand molecules

The steps involved in obtaining Catecholamine molecules, from PRODRG server, were shown in Fig. 1. The other