**Parkinson’s disease** is a common neurodegenerative disease. The vast category of neurodegenerative diseases includes Alzheimer disease, Parkinson’s disease, Huntington disease, and amyotrophic lateral sclerosis. These devastating illnesses are characterized by the progressive loss of selected neurons in discrete brain areas, resulting in characteristic disorders of movement, cognition, or both. For example, Alzheimer disease is characterized by the loss of cholinergic neurons in the *nucleus basalis* of Maynert, whereas Parkinson disease is associated with a loss of dopaminergic neurons in the *substantia niagra*. The most prevalent of these disorders is Alzheimer, affecting some four million people. Parkinson disease is the second most frequent disorder, affecting approximately 1.5 million Americans (Richard *et al.*, 2006).

The careful observations of James Parkinson on six patients with “shaking palsy” resulted in the publication in 1817 of an essay that has become a classic in the history of medicine. He differentiated a triad of symptoms, including involuntary tremor of the limbs, rigidity of muscles, and slowness of movement, since then that has been called Parkinson’s disease, or Parkinsonism. There are almost 1.5 million cases of Parkinson’s disease in the United States, with 50,000 new cases being diagnosed each year. The disease is almost exclusively seen in patients 50 to 70 years of age. Most cases of Parkinsonism are unknown origin (idiopathic Parkinsonism). Idiopathic Parkinsonism has been considered to be a part of the aging process that is associated with the loss of neurons. A threshold number of neurons are required for smooth functioning of the muscles (Charles and Stitzel, 1997).

Epidemiology of Parkinson disease in the city of Kolkata, India: a community-based study showed that the age-adjusted prevalence rate (PR) and average annual incidence rate were 52.85/100,000 and 5.71/100,000 per year, respectively. The adjusted average annual mortality rate was 2.89/100,000 per year. The relative risk of death was 8.98. The case-control study showed that tobacco chewing protected and hypertension increased PD occurrence (Das *et al.*, 2010).

The Parsi community of Mumbai, India has a prevalence of Parkinson’s disease of 328.3 per 100,000 populations, which is almost in excess of that found in Nebraska. This is despite India as a whole having a low prevalence due to the inhalation of Aspand seed fumes, as a part of their religion. Aspand seed is the richest
natural source of two MAO Inhibitor alkaloids, harmine and harmaline, used in Parkinson's disease. Long term use of MAO inhibitors, eventually has the opposite effect, and so may cause the high prevalence of Parkinson's disease amongst the Parsi (viartis.net, 2012).

There are some types of Parkinsonism for which the cause is known. Postencephalitic Parkinsonism was the result of late-onset complications of encephalitis lethargica, short-lived viral encephalitis which occurred in early 1900s. Fortunately, this form of Parkinsonism is no longer seen. Iatrogenic Parkinsonism is a frequent adverse side effect of most antipsychotic drugs. Parkinsonism is also known to result from arteriosclerosis, manganese poisoning, carbon monoxide poisoning, and hepatolenticular degeneration (Wilson’s disease). Dr. James Parkinson's astute evaluation of several of his patients who demonstrated similar involuntary tremors in their arms and/or legs led to his publishing an article that is now considered a milestone in clinical diagnosis. It describes a disease that now bears his name (Charles and Stitzel, 1997).

Typically, the disorder presents in mid- or late life, with onset ranging from 40 to 80 years and most likely at 55-65 years; cases of early onset before age 40 are less common, and rare juvenile cases have also been reported. PD presents as a classic tetrad of signs which includes (a) Resting tremor that improves with voluntary activity, (b) Bradykinesia or slowness of initiating voluntary movements, (c) Rigidity of muscle and joint motility, (d) Postural disturbances including falls.

These signs vary in their early intensity, combinations, and progression among individuals. The motor disabilities characterizing PD are primarily due to the loss of dopaminergic neurons in the substantia nigra resulting in a dramatic decrease of dopamine levels in the brain. Once the DA neuronal cell death reaches the critical level of 85-90%, the neurological symptoms of PD appears neuropathologically. PD is a slowly progressive neurodegenerative disorder of unknown cause that selectively affects the extra pyramidal DA nigrostriatal pathway. The disease is characterized by gradual destruction of DA-containing neurons in the pars compacta component of the pigmented mid brain substantia nigra, leading to a deficiency of the neurotransmitter in DA nerve terminals of the corpus striatum, particularly in the putamen (Abraham, 2003).
Neural control of locomotion can be voluntary or involuntary. Involuntary locomotion can occur using only the spinal cord circuitry, as in reflex movements, or stereotyped behaviour. In fact, spinal circuitry is able to produce functional locomotor movements and can be utilized to aid in mobility after spinal cord injury (Fouad and Pearson, 2004). However, voluntary locomotion, similar to any voluntary movement, requires cortical interaction with the basal ganglia. In particular, any type of planned motor output or movement involves activation of the basal ganglia prior to the movement(s) being executed. Therefore, if any part of the basal ganglia are not functioning properly, the motor commands will not be produced in the intended way or possibly will not be produced at all (DeLong, 2000). These pathways, many of which are dopaminergic, are highly conserved among mammals (DeLong, 2000).

![Diagram of the basal ganglia](image)

**Figure 1.1** Diagrammatic representation of the working of the basal ganglia in a normal and Parkinsonian brain. The two types of dopamine receptors (D1, D2) are located on two types of output pathways. Internal segment of the *globus pallidus* (GPi); External segment of the *globus pallidus* (GPe); *Substantia nigra* pars compacta (SNC); *Substantia nigra* pars reticulate (SNR); *Subthalamic nucleus* (STN).
The *striatum*, the *globus pallidus*, the *substantia nigra* (pars compacta and pars reticulata), and the *subthalamic nucleus* are the structures that make up the basal ganglia (Figure 1.1). These four nuclei are located throughout the forebrain and midbrain and play a major role in the initiation of voluntary movement (DeLong, 2000). The *striatum*, often referred to as the striatum-putamen, consists of the *caudate nucleus*, the *putamen*, and the ventral striatum (nucleus accumbens). The striatum is the main input target of the basal ganglia. These inputs come from the cerebral cortex, thalamus and brainstem. The main output of the basal ganglia arises from the *substantia nigra* (SNR) and the *globus pallidus* and is inhibitory to the thalamus. The internal circuitry of the *basal ganglia* is illustrated in Figure 1, as follows. The neurons of the striatum project to the *globus pallidus* and the *substantia nigra* which in turn project to the thalamus and brainstem, via two pathways, termed the direct and the indirect pathways. The direct pathway facilitates movement. It projects directly from the striatum to the output nuclei, i.e. *globus pallidus* (Gpi) and *substantia nigra* (SNR). This pathway allows the momentary activation of the thalamus and brainstem pathways by inhibiting the tonically active inhibitory neurons which project to the thalamus and brainstem. The indirect pathway, which inhibits movement, also begins at the *putamen* and runs through the external segment of the *globus pallidus* (GPE) and secondly from the *subthalamic nucleus* (STN) to the output nuclei via a rare glutaminergic excitatory pathway. Activation of this pathway ultimately results in the inhibition of the thalamus and brainstem (DeLong, 2000).

These two pathways of the striatum are differentially acted upon by the dopaminergic input from the *substantia nigra* pars compacta (SNC). Striatal neurons of the direct pathway normally receive excitatory input from dopaminergic neurons in the *substantia nigra* pars compacta. This activity acts through D1 type dopaminergic receptors. Conversely, dopaminergic input from the *substantia nigra* pars compact inhibits the indirect pathway, by acting through D2 receptors on striatal neurons. This input also facilitates movement by inhibiting the inhibitory indirect pathway. In Parkinson’s disease, the lack of dopaminergic input from the *substantia nigra* due to reduced numbers of dopaminergic neurons results in reduced excitation of the excitatory direct pathway and reduced inhibition of the inhibitory indirect pathway, causing reduced movement. In summary, Parkinson’s disease results in an overactivity of the basal ganglia output nuclei, resulting in net decrease in movement.
Nearly 40 years after levodopa or L-dopa introduction, remains an effective Pharmacotherapy in Parkinson’s disease. Development of L-dopa as a therapeutic agent in PD is a rare example of a rationally predicted and logically pursued clinical treatment in a neurological disorder, based on neurochemical pathology and basic Pharmacological theory. The effectiveness of L-dopa treatment requires its penetration into the central nervous system (CNS) and local decarboxylation to DA.

Although L-dopa reduces many of the motor symptoms of PD, it does not affect non-motor symptoms and does not halt the progression of the degeneration of dopamine containing neurons in the substantia nigra (Wolters, 2000). Progression of Parkinson’s disease advances (4-8 years), the efficiency of L-dopa decreases over time such that many patients develop motor fluctuations (‘wearing-off’ and ‘on-off’ phenomena) and dyskinesias, and patients no longer exhibit a stable and predictable clinical response (Marsden and Parkes, 1976). Therefore, increasing amounts and frequencies of dosing of L-dopa are usually necessary to maintain the initial therapeutic response (Rinne, 1983). It has also been postulated that L-dopa could be toxic to dopamine containing neurons (Fahn, 1997). The therapeutic advantages and disadvantages of early versus delayed tretment with L-dopa are still debated (Fahn, 2004).

The development of a new drug involves three approaches (1) The general screening approaches in which chemical substances from any source are tested for their effect against predetermined disease or disease state, (2) The chemical modification of existing drug substance whose biological effects are known and (3) Mimicking the nature by biochemical design, where a compound is made to exert an action in a manner similar to a known biochemical substance. Any lead compound obtained from these three approaches is usually further modified chemically to gain the biologically most potent representative of the series.

In the recent scenario, advances have taken place in the field of prodrug approach of dopamine to ensure whether dopamine conjugates with various amino acids are able to cross the blood brain barrier, so that the use of levo-dopa as the precursor of dopamine could be reduced, thus minimizing the side effect of levo-dopa. Levo-dopa has the most tremendous side effects. The literature survey reveals that not much work has been done on dopamine conjugation with amino acids and peptides.
Such peptides may be comprised of units, which themselves are the part of various physiological processes. Such a conjugation may be helpful for the formulation of the targeted drug delivery systems of dopamine in the brain.

The present study envisages to synthesize and evaluate some amino acids and peptide conjugates of dopamine and to investigate:

- Synthesis of Dopamine conjugates with hydrophobic amino acids.
- Synthesis of Dopamine conjugates with molecules with increasing number of carbon between NH$_2$ and COOH.
- Synthesis of Dopamine conjugates with dipeptides.
- Structural elucidation of synthesized compounds by means of spectral studies.
- Whether these conjugates will facilitate the entry across BBB.
- Evaluation as anti-Parkinson’s activity by two animal models:
  (a) Oxotremorine induce tremor in mice model and
  (b) 6-OHDA or hemi-Parkinsonian rat model.