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Review

Dopamine in Parkinson's disease

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ABSTRACT

Parkinson's disease is a neurodegenerative disease caused by the death of neurons, ie, cells critical to the production of dopamine, an important neurotransmitter in the brain. Here, we present a brief review of the dopamine synthetic pathway, binding to the dopamine receptors, and subsequent action. The production of dopamine (a monoamine neurotransmitter) occurs in the ventral tegmental area (VTA) of the substantia nigra, specifically in the hypothalamic nucleus and midbrain. Compared to other monoamines, dopamine is widely distributed in the olfactory bulb, midbrain substantia nigra, hypothalamus, VTA, retina, and the periaqueductal gray area. Dopamine receptors are large G-protein coupled receptor family members, of which there are five subtypes including D1, D2, D3, D4, and D5. These subtypes are further divided into two subclasses: D1-like family receptors (types 1 and 5) and D2-like family receptors (types 2, 3, and 4). Four different pathways and functions of the dopaminergic system are presented in this review. In the oxidation of dopamine, 5,6-indolequinone, dopamine-o-quinone, and aminochrome are formed. It is difficult to separate the roles of 5,6-indolequinone and dopamine-o-quinone in the degenerative process of Parkinson's diseases due to their instability. The role of aminochrome in Parkinson's disease is to form and stabilize the neurotoxic protofibrils of alpha-synuclein, mitochondrial dysfunction, oxidative stress, and the degradation of protein by lysosomal systems and proteasomes. The neurotoxic effects of aminochrome can be inhibited by preventing the polymerization of 5,6-indolequinone, dopamine-o-quinone, and aminochrome into neuromelanin, by reducing aminochrome catalysis by DT-diaphorase, and by preventing dopamine oxidative deamination catalyzed by monoamine oxidase. In addition to these, the conversion of dopamine in the neuromelanin (NM) shows both protective and toxic roles. Therefore, the aims of this review were to discuss and explain the role of dopamine and explore its physiology and specificity in Parkinson's disease, as well as its role in other physiological functions.

1. Introduction

Dopamine is a brain hormone that acts as a neurotransmitter. It is produced in the brain in an area called the substantia nigral. It is also produced in other parts of the brain such as the ventral tegmental area and hypothalamus. $C_8H_{11}NO_2$ is the chemical formula of dopamine. Different nervous system diseases are attributed to the abnormal function of dopamine. Dopamine in the brain increases due to the action of drugs and in response to happiness. The brain controls body movements through the action of dopamine [1,2]. By understanding how dopamine regulates the function of the brain in controlling body movement, we may identify some important treatments for brain-related diseases such as Parkinson's disease (PD) and some psychiatric disorders. The social importance of dopamine as a brain neurotransmitter plays a vital role in

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matters of abuse linked to need and habits. In living patients, positron emission tomography (PET) is used to demonstrate the availability of dopaminergic ligands and the loss of dopamine in PD patients [3,4,5].

There are five subtypes of dopamine receptors including D1, D2, D3, D4, and D5, which are a superfamily of receptors coupled to a large protein (G-protein) [6,7]. These subtypes are further divided into two subclasses, D1-like family receptors (types 1 and 5) and D2-like family receptors (types 2, 3, and 4). The drug sensitivity and structure of type 1 and type 5 are similar, whereas types 2, 3, and 4 only have similar structures. The Gs and Gi-mediated transduction systems are coupled to [8] dopamine receptors [9]. There are four major pathways in the dopaminergic system, the nigrostriatal, mesocortical, tuberoinfundibular, and mesolimbic pathways [10]. The role of dopamine is to regulate movement and it also plays a crucial role in reward system. The ventral tegmental area (VTA) is a nerve cell area where dopamine is produced in the reward pathway. From the VTA, dopamine is released into the prefrontal cortex and nucleus accumbens [11,12]. Dopamine is produced in the substantia nigra cell bodies and released into the striatum for motor functions. The different functions of dopamine include inhibiting the production of prolactin, movement, behavior, motivation, punishment, learning, reward, cognition, attention, dreaming, working memory, mood, and sleep [13,14]. In the synthesis of catecholamines like norepinephrine and epinephrine, dopamine plays a precursor role [15].

Dopamine is synthesized by tyrosine. It is then taken up by an active transport mechanism in the brain. Tyrosine is produced from phenylalanine in the liver via phenylalanine hydroxylase. Gene therapy and other modalities for treatment can be improved by targeting the regulatory mechanism of tyrosine hydroxylase [16]. When dopamine is synthesized, it enters the synaptic vesicles with the help of vesicular monoamine transporter 2 (VMAT2). It is then stored there and released by exocytosis into the synapses [17,18]. This review highlights the recent research on dopamine and the dopaminergic system and their physiological roles and function. In addition, the dysregulation of the dopaminergic system that induces PD is discussed, as well as the implication of dopamine in other pathologies.

2. Dopamine receptors

2.1. Receptors and types

Dopamine is a chemical, which is also a brain hormone. It transmits signals within the brain. Some brain cells produce it and then secrete it to bind to the target and exert its effects [19]. Dopamine functions through five different receptors. These receptors act as a lock and DP is the key to these receptors. Dopamine is released from one cell and binds to other cells through these receptors [20]. Hence, dopamine transmits a signal from one neuron to another neuron and is called a neurotransmitter [21,22].

Dopamine receptors are divided into two major subclasses:

- The D1-like family (type 1 and type 5 have similar structures and drug sensitivities).
- The D2-like family (type 2, type 3, and type 4 have similar structures) [23].

The activity of adenyl cyclase is stimulated by the presence of dopamine and dopamine receptors. In a study on brain antipsychotic drugs, Seeman et al. labeled a brain site with dopamine and reported that binding was inhibited by nanomolar concentrations of unlabeled haloperidol. This site was later called the D2 receptor of dopamine [7, 24,25]. The opening of Na channels or the excitation and closing or inhibition of K channels causes the activation of the D1-like family of receptors. Inhibition of the targeted neurons is the final effect of activation of the D2-like family. The effect of dopamine on a target neuron depends upon the internal of secondary messenger cyclic AMP in these neurons and upon the different types of receptors present on this neuronal membrane. D1 receptors are the most abundant dopamine receptors in the human's nervous system of and D2 receptors are the second most abundant receptors. The lower-level receptors include D3, D4, and D5 [23,26,27].

D1 and D5 are primarily involved in postsynaptic inhibition and D2, D3, and D4 are involved in presynaptic and postsynaptic modifications. Mood regulation and the control of movement by the basal ganglia and emotion stabilization by the limbic system are the functions of D2 receptors [28]. D1 and D2 receptor differences are due to different effector mechanisms, different antagonist and agonist-binding affinities, and also on different distribution patterns in the central nervous system. The therapeutic efficiency of antipsychotic drugs is more closely related to D2 receptors as these receptors show more affinity for these drugs. Thus, they are considered the most important antipsychotic drug action sites [29,30].

The affinity of the D1 receptor is high for antagonist SCH 23,390 and low for butyrophenones such as haloperidol. The formation of cAMP is dependent upon stimulation of the activation of the D1 receptor. However, the opposite effect is seen with D2 receptors. The turnover of phosphoinositide is also stimulated by the D1 receptor, as is the modulation of intracellular Ca levels [8]. There is a high concentration of D1 receptors in the nucleus accumbens, olfactory tubercle, hippocampus, substantia nigra pars reticulata, caudate, putamen, hypothalamus, and temporal and frontal cortexes. Cognitive functions like memory and attention controlled by dopamine involve D1 receptors. The central nervous system effects of cocaine significantly involve D1 receptors and the effect of drugs of abuse involve the D2 receptors and other receptors [24,31].

D1 receptors are similar to D5 receptors but different than D2, D3, and D4 receptors. D1 receptors are about 50% homologous to D5 receptors. As these two receptors are structurally similar, their affinity for different types of dopaminergic drugs is similar. The only feature that distinguishes D1 and D5 receptors is the stronger dopamine binding affinity of D5 receptors compared to D1 receptors. D5 receptors are expressed in the hypothalamic nucleus. D5 receptors play a role in pain process [18,32,33]. D2 receptors are present in the nucleus accumbens, spectrum, VTA, and basal ganglia. The positive influences of dopamine are mediated by D3 receptors in neurotensin production. D4 receptors are 41% homologous to D2 receptors and about 39% to D3. They are present in the frontal cerebral cortex and hippocampus [34].

The primary target of antipsychotic drugs has been considered D1-like receptors, but these are now considered irrelevant for these drugs. Among the three D2-like receptors, D2 receptors have been directly associated with antipsychotic drugs and are blocked by them [8,35]. D1 receptors convert adenylate cyclase to cyclic AMP (secondary messenger) upon activation. D2 receptors inhibit adenylate cyclase as it is not positively linked to this enzyme. The mediation of extrapyramidal and behavioral activity is done by D2 receptors (postsynaptic receptors). D2 receptors blocked by neuroleptics (therapeutically effective) and are activated by bromocriptine (receptor agonist) which is used to treat PD. There is a correlation with a series of neuroleptics in the brain, which show an antagonist effect [29,36].

The synthesis of cyclic AMP is followed by DARPP-32, which is known as dopamine and AMP regulates phosphoprotein, which is phosphorylated by stimulation with D1 receptor agonists. Dopamine agonist binding affinity does not depend upon the degree of the association of the receptor and guanine-binding protein (regulatory), which is regulated by GTP and Ca or Mg ions. The agonist affinity of D1 receptors varies depending upon the balance of divalent cations, which promotes high affinity, and GTP, which promotes low affinity. D5 receptors are considered high-affinity D1 [29], D3, and D4 receptors are present only in limbic areas of the human brain and rat brain. These receptors have a high affinity for atypical neuroleptics such as clozapine. Mediation of

the antipsychotic action of typical and atypical neuroleptics by the human brain involves D3 and D4 receptors. The development of neuroleptics has involved targeting these receptors restricted to the limbic system [34,37,38].

2.2. D1-like dopamine receptor expression and function

The cortex, striatum, and limbic system of the brain and the cardiovascular system contain D1-like dopamine receptors. This receptor also regulates neuronal growth. Our behavior is also controlled by this receptor. When we learn something, this receptor is active during the learning process. During locomotor activities and some acts of happiness or reward, this receptor is activated and binds dopamine. It also regulates the activity of the D2 receptors. The D1 receptor also plays a role in memory [39,40,41]. When dopamine is bound to the D1 receptor, guanosine nucleotide-binding proteins (G proteins) are activated, and adenylyl cyclase (AC) activity is stimulated, which generates a cyclic AMP molecule that acts as a secondary messenger. Other signaling pathways also include DI receptors, which are involved in the release of phospholipase C and calcium ions (Fig. 1 and Table 1). These ions are very important for the activation of some proteins such as calcium-dependent protein kinase C (PKC). The electrochemical gradient is adjusted by the D1 receptors through Na^+ K^+ ATPase. In the kidney and striatum, the activation of D1 receptors also inhibits Na^+ K^+ ATPase through the protein kinase A (PKA) and PKC signaling pathways [27,42].

2.3. D2-like dopamine receptor expression and function

The D2 receptor subfamily includes D2, D3, and D4. D2 short and D2 long-type receptors are the two isoforms. This receptor is present in the amygdala, striatum, and hippocampus, pituitary, and septal region along the VTA and SN of dopaminergic neurons. When dopamine is bound to the D2 receptor, the D2 receptor is activated, and it is totally opposite to the D1 receptor. AC activity is inhibited by the activation of this receptor. When AC is not activated, cAMP is not activated and PKA levels drop. This receptor usually controls behavior. The D2 receptor is an auto-receptor, and it usually stops dopamine synthesis and inhibits the release of dopamine from the cells (Fig. 2 and Table 1). In the embryonic stage, the D2 receptor plays a role in the development of dopamine neurons [40,44].

2.4. D2 receptors are G protein-coupled receptors

G protein-coupled receptors (GPRCs) contain seven segments, with an amino (N) terminal outside the cell and a carboxyl (C) terminal within the cell. One loop is larger than the others and the G protein is attached to that loop. Three protein subunits α, β, and γ comprise G protein. The βγ subunit helps the G protein enter the membrane of the cell. G proteins are classified into two classes:

- Gαs
- Gαi

2.4.1. G protein structure

D2 receptors bind to two classes of G protein, Gαi and Gα0. When the ligand is bound to G protein, guanosine diphosphate (GDP) is changed to guanosine triphosphate (GTP) by the Gα proteins, and the α-subunit separates from the remaining subunits (Figs. 3 and 4 and Table 1). At this stage, the three subunits are ready to transfer the signal. Gαi and Gαo inhibit cyclic AMP production by stopping AC activation, which leads to a decrease in the level of PKA [45,46,47].

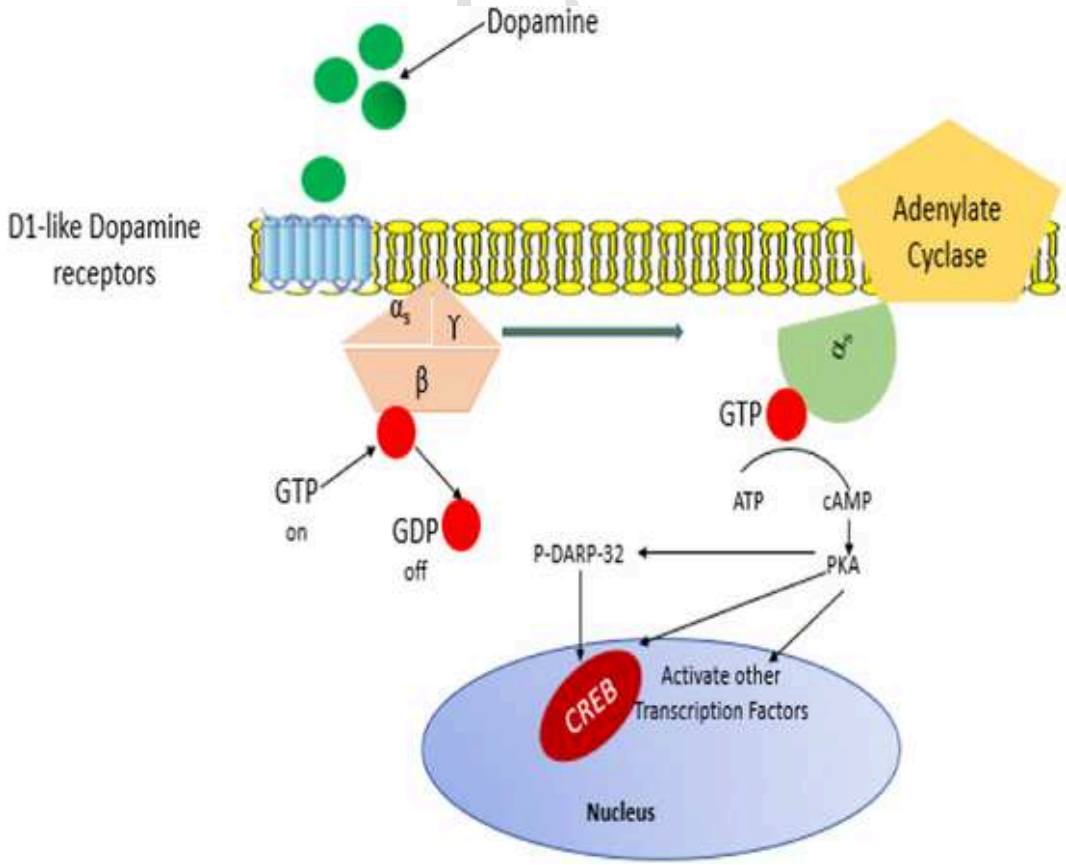

Fig. 1. Schematic representation of a D1-like receptor [43].

Table 1
Dopamine receptor location and function.

Receptor	Location	Function
D1	1. High concentrations of D1 receptors in mesocortical (striatum, nucleus accumbens, substantia nigra, caudate, olfactory bulb, and putamen), mesolimbic and nigrostriatal areas. 2. Found in low concentrations in hypothalamus, cerebellum, kidney, cerebellum, thalamus, and hippocampus.	Feeding regulation Reward Control impulse Sleep Affect Voluntary movements Reproductive behavior Learning Rennin control in kidney Growth and development regulation Attention Working memory
D2	1. Found in high concentrations in olfactory bulb, putamen, substantia nigra, VTA (ventral tagmental area), caudate and nucleus accumbens. 2. Found in low concentrations in kidneys, blood vessels, hypothalamus, heart, gastrointestinal tract, septum, sympathetic ganglia, cortex, and adrenal glands.	Blood pressure regulation Motivation Vasodilatation Regulation of locomotion (locomotion inhibition by presynaptic receptors but postsynaptic receptors are involved in inactivation of locomotion) Working memory Renal function Gastrointestinal motility
D3	Present only in the central nervous system, not outside the central nervous system. Also present in nucleus accumbens and olfactory bulb.	Cognition function Modulation of endocrine function Regulation of locomotion Emotion
D4	Present in thalamus, frontal cortex, gastrointestinal tract, blood vessels, substantia nigra, heart, hippocampus, kidney, amygdala, globus pallidum, adrenal glands, sympathetic ganglia, and hypothalamus. The lowest number of receptors are found in the central nervous system.	Vasodilatation Renal function regulation Blood pressure Gastrointestinal motility Cognitive function modulation
D5	Found in hippocampus, substantia nigra, kidney, hypothalamus, dental gyrus, blood vessels, gastrointestinal tract, heart, adrenal glands, and sympathetic ganglia.	Endocrine function Affective functions Pain process

3. Pathways of the dopaminergic system

3.1. Pathways of dopamine formation

There are four main pathways of dopamine formation, the nigrostriatal, mesocortical, tuberoinfundibular, and mesolimbic pathways.

3.1.1. Nigrostriatal pathway

This is the main pathway, which is directly linked to PD. The nigrostriatal pathway starts from the substantia nigral part of the brain and ends in the part called the caudate putamen. D1 and D2 receptors are present in this dopamine pathway. Both receptors are postsynaptic but the D2 receptors are also presynaptic. There are direct and indirect pathways in the brain that start from the motor cortex and return back to the motor cortex via the thalamus (Fig. 5). These two pathways are regulated by these two receptors [48,49].

The D2 receptor usually inhibits the auto-receptors, and antagonists of these receptors increase the production of dopamine. One example of such an antagonist is haloperidol. Tardive dyskinesias can develop from the use of these drugs.

Excess dopamine production by this pathway results in:

- Chorea (Huntington disease)
- Athetosis
- Tics
- Decreases in dopamine production, which may lead to PD

Important functions of dopamine are involved in movements like learning new motor skills and controlling motor functions. PD is due to the disintegration of the nigrostriatal system. Ascending projections from the cell bodies release dopamine to the dorsal striatum, particularly to the putamen and caudate, to modulate motor control. Abstraction of the nigrostriatal dopamine receptors due to antipsychotic drugs causes extrapyramidal effects [34,50,51].

3.1.2. Mesocortical pathway

In this pathway, dopaminergic fibers originate in the VTA or A10 region and end in the septohippocampal region and frontal cortex. These fibers function in emotional and cognitive behavior. Improvements in memory and attention are due to dopamine levels in the brain, particularly the prefrontal cortex. However, memory problems are associated with high or low levels of dopamine. Increases in the negative symptoms of schizophrenia occur due to the use of antipsychotic drugs, which block the dopamine receptors in this pathway [52,53].

3.1.3. Mesolimbic pathway

In this pathway, dopaminergic projections start from the VTA and end toward the VTA, amygdala, nucleus accumbens, and pyriform cortex. This pathway functions in reward and emotion. Pleasure is also mediated by this system. Mesolimbic dopamine is released during pleasurable situations, which also stimulates pleasure-seeking, explaining why the release of dopamine in the brain, especially in the nucleus accumbens and prefrontal cortex, from eating, drugs, and sex occurs. The activation of this pathway is due to the abuse of several drugs, and it is thought that plastic changes in the mesolimbic pathway cause drug addiction. Decreases in the positive symptoms of schizophrenia that occur due to the use of antipsychotic drugs cause obstruction of the dopamine receptors in this pathway [54,55,56].

3.1.4. Tuberoinfundibular pathway

This pathway starts from the paraventricular and arcuate nucleus of the hypothalamus and ends at the median eminence (pituitary gland). Inhibition of the release of prolactin by dopamine occurs via this pathway. Antipsychotic drugs disinhibit prolactin release and also cause galactorrhea. The major neuroendocrine inhibitor of prolactin secretion is dopamine. The release of dopamine from the hypothalamus nucleus to the hypothalamohypophysial blood vessels of the median eminence, which supplies blood to the pituitary gland, acts on the prolactin-producing cells of the lactotroph (produce prolactin in the absence of dopamine). Thus, dopamine is also known as prolactostatin, PIF (prolactin-inhibiting factor), or PIH (prolactin-inhibiting hormone) [57,58,59,60] (Table 2). Reward and movement regulation are accomplished by the brain through this pathway. Increases in dopamine via this pathway result in:

- Psychosis
- Euphoria
- Hallucinations
- Schizophrenia

3.2. The direct and indirect pathways

These two pathways are involved in the regulation of movement in the basal ganglia and oppose each other. The direct pathway is a positive movement pathway as it boosts movement while the indirect pathway has a negative effect on movement, inhibiting movement [61,62,63].

PD is related to a defect in the direct pathway (Fig. 6). Any defect in the direct pathway inhibits body movement and the signal from the indirect pathway gets stronger and slows down or completely stops movement, which gives rise to PD [64,65].

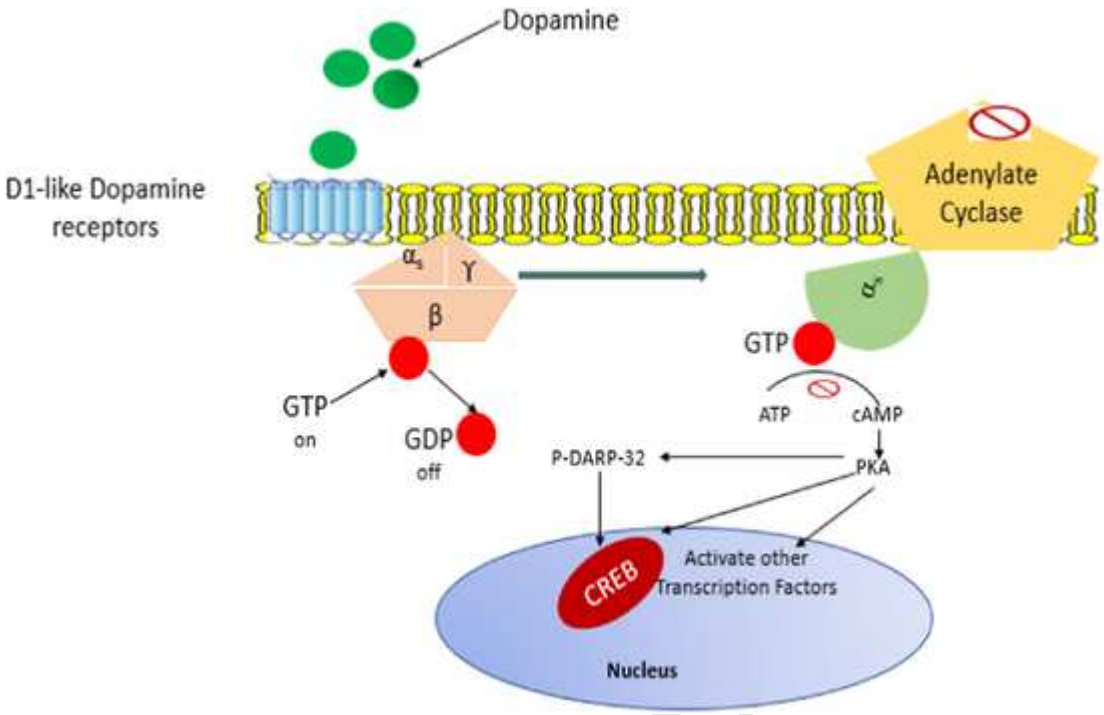

Fig. 2. Schematic representation of a D2-like receptor [43].

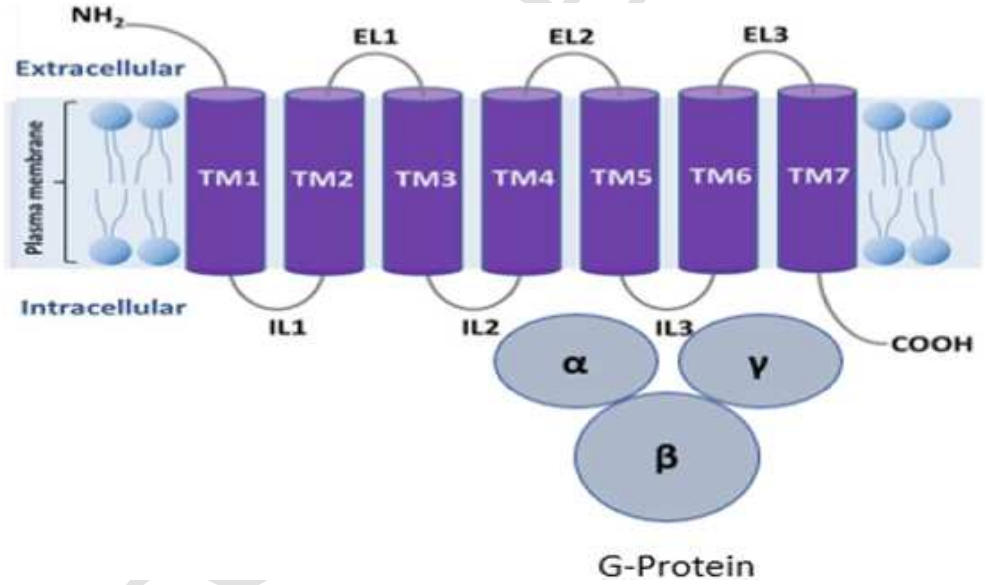

Fig. 3. G protein structure [46].

Both pathways are related to the thalamus but have totally different effects on the thalamus. The thalamus is related to body movement and the direct pathway excites body movement, so it leaves the thalamus excited and active. The indirect pathway inhibits body movement, so it leaves the thalamus inactive and inhibits its function. The direct and indirect pathways send signals to the thalamus and then the thalamus either sends inhibitory or excitatory messages to the cortex for movement regulation [66].

4. Dopamine metabolism

4.1. Dopamine synthesis and storage

The activation of movement is done by dopaminergic neurons and dopamine is produced in these neurons. After dopamine synthesis and storage, it is released into the synaptic space. Although dopamine is produced in the cytosol of neurons, it cannot be stored within the cytosol because the pH of the cytosol is high (7.1) and dopamine is oxidized at high pH values. Oxidation is due to the detachment of the proton from the hydroxyl group of dopamine at high pH. Therefore, it is necessary to shift dopamine into monoaminergic synaptic vesicles by the dopamine transporter vesicular monoamine transporter (VMAT-2). This prevents the accumulation of dopamine in the cytosol [67,68]. In

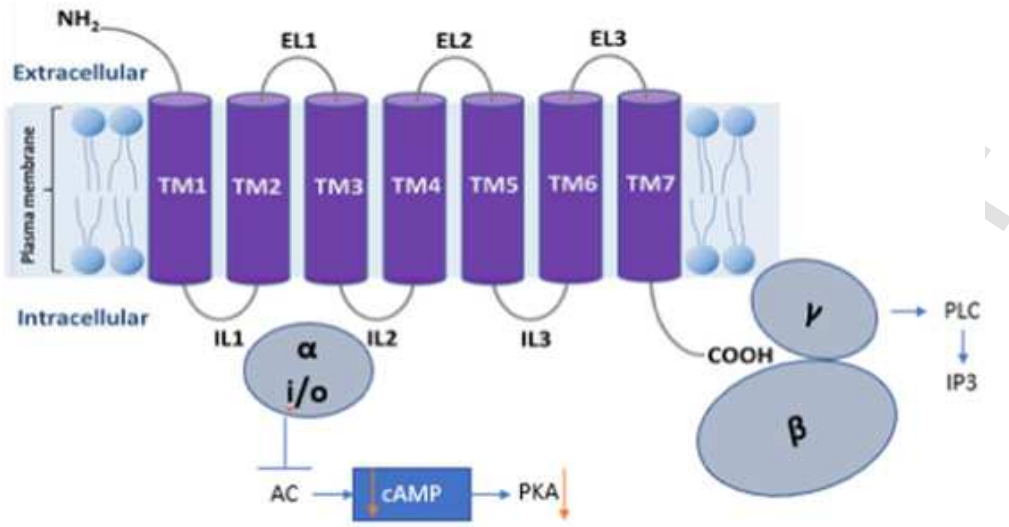

Fig. 4. D2 receptors: intracellular signaling [46] (illustration is simplified for didactic purposes).

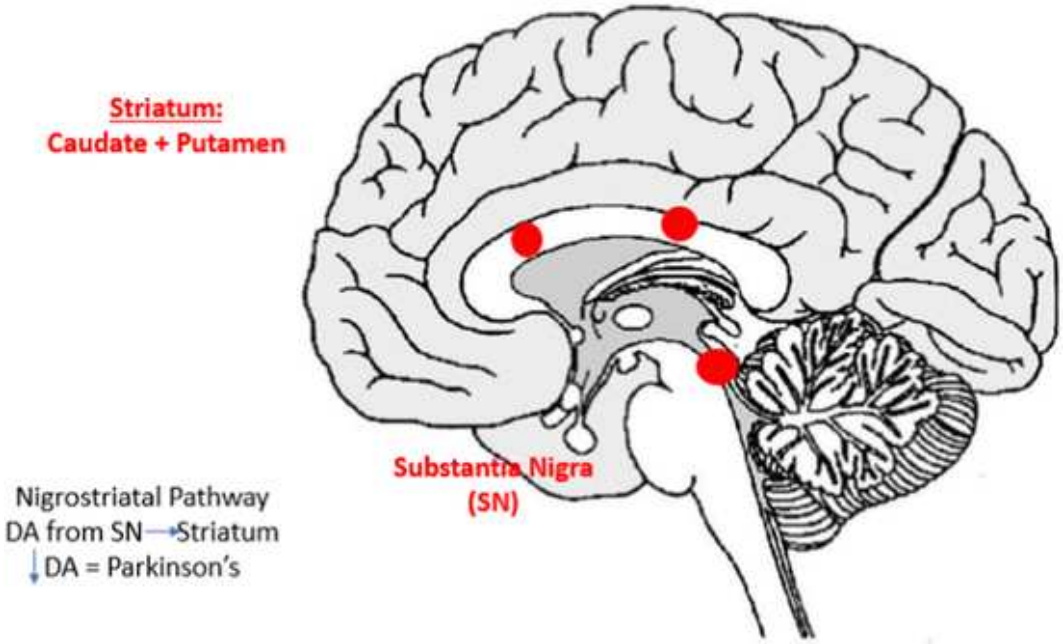

Fig. 5. Nigrostriatal dopamine pathway.

Table 2
Dopamine pathways and major functions.

Pathway	Function
Nigrostriatal	Sensory stimuli and movement
Mesocortical	Learning, memory, emotional behavior, cognition, and attention
Mesolimbic	Addiction, perception, pleasure, emotion and behaviors like reward-seeking
Tuberoinfundibular	Prolactin inhibition and control of the pituitary endocrine system of the hypothalamus

these vesicles, dopamine is stored for a long time without oxidation. Dopamine in these vesicles is not oxidized because the pH of these vesicles is low (2.0 – 2.4). At low pH values, the proton of the hydroxyl group is strongly attached to dopamine and dopamine remains stable. VMAT-2 is present within the membrane of these vesicles. Due to vesicular monoamine transporter VMAT-2-coupled vesicular ATPase, the pH of these vesicles is low because the hydrolysis of ATP to ADP releases one inorganic phosphate and proton, creating a proton gradient and lowering the pH of the monoaminergic vesicles. Dopamine oxidation is also prevented by the important complex (TH-AADC-VMAT-2). The amino acid tyrosine is the precursor of dopamine synthesis. Dopamine is synthesized from tyrosine in two steps with the help of tyrosine hydroxylase (TH) and aromatic amino acid decarboxylase (AADC) (Fig. 7) [69,70,71,72].

- Hydroxylation occurs and tyrosine is changed to l-dihydroxy phenyl aniline (L-dopa) by tyrosine hydroxylase (TH). This reaction requires oxygen.
- The second step is decarboxylation. L-dopa is then converted to dopamine by aromatic amino acid decarboxylase (AADC). CO_2 is produced by this enzyme.

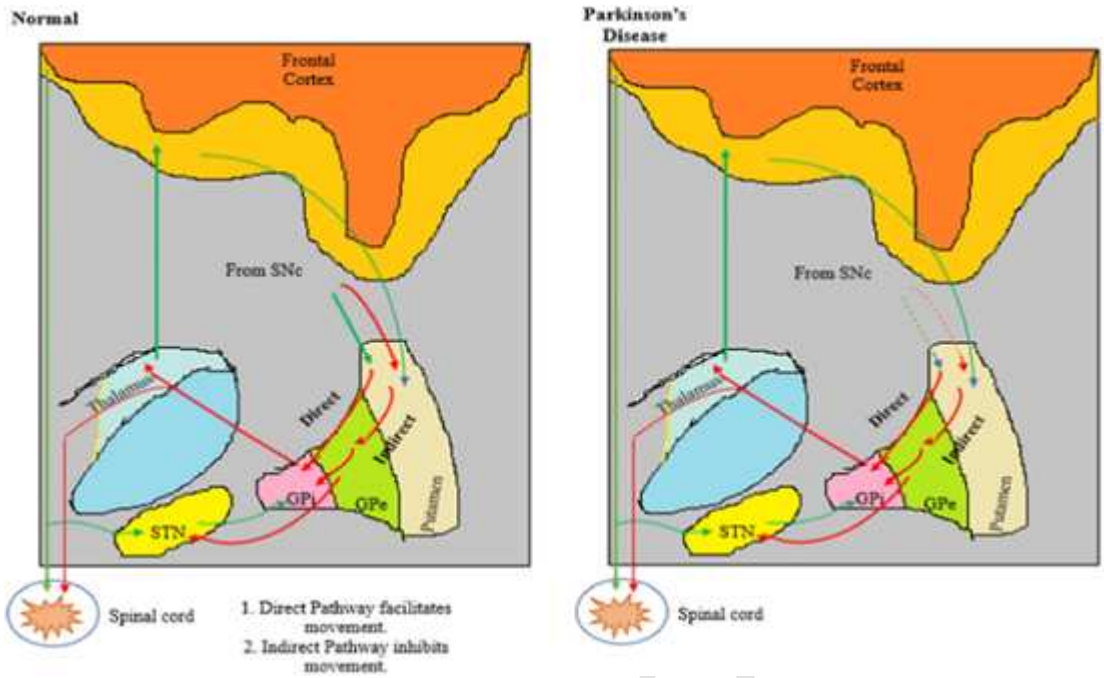

Fig. 6. Excitatory signals and inhibitory signals in the basal ganglia in a normal brain and one with PD.

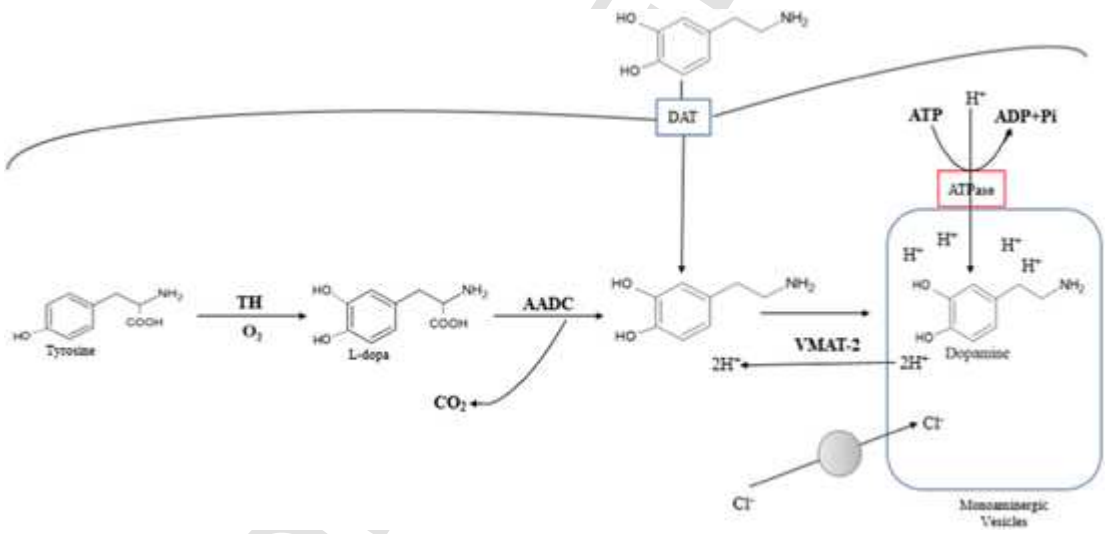

Fig. 7. Storage and synthesis of dopamine in a neuron.

4.2. Metabolism of dopamine

Two important enzymes are needed for the metabolism of dopamine, catechol-O-methyl transferase (COMT) and monoamine oxidase (MAO). Dopamine is changed to its inactive metabolites by these enzymes. MAO has two subunits, MAO-A and MAO-B. Astrocytes contain MAO-B while MAO-A is present in the catecholaminergic neurons as cells of the system nervous. And the glial cells secrete COMT. Neurons have a very low level of or lack this enzyme. Dopamine is first converted to 3,4-dihydroxyphenylacetaldehyde (DOPAL) by MAO. DOPAL is then converted to 3,4-dihydroxyphenylacetic acid (DOPAC) by aldehyde dehydrogenase [73,74] (Fig. 8).

The other pathway of metabolism is through the enzyme COMT. In this pathway, dopamine is converted to 3-methoxytyramine (3MT). 3-MT is further reduced to homovanillic acid (HVA), which is eliminated in urine. MAO inhibition has been used as adjunctive therapy in brain-related illnesses such as PD [75]. However, the inhibition of MAO only raises the level of dopamine and cannot decrease H_2O_2 production·H_2O_2 production is maintained by different systems in the neurons such as catalase and glutathione. And H_2O_2 is less toxic than the DOPAC metabolites. When dopamine levels are decreased in different parts of the brain, it is taken up again by the DAT system and MAO breakdowns the dopamine into DOPAC. Few DATs are present in neurons. Norepinephrine transporter (NET) on nearby neurons provides another pathway for dopamine breakdown by COMT. Dopamine degradation is faster by the DAT pathway than by NET [76,77,78] (Fig. 9).

4.3. Dopamine oxidation to dopamine-o-quinone and its cyclization to aminochrome

At high pH and in the presence of oxygen dopamine is oxidized to o-quinones in the absence of metal ions. Dopamine is oxidized to aminochrome. Fig. 10 shows that in the reaction, one oxygen is reduced to a superoxide radical, so dopamine is converted to dopamine-o-

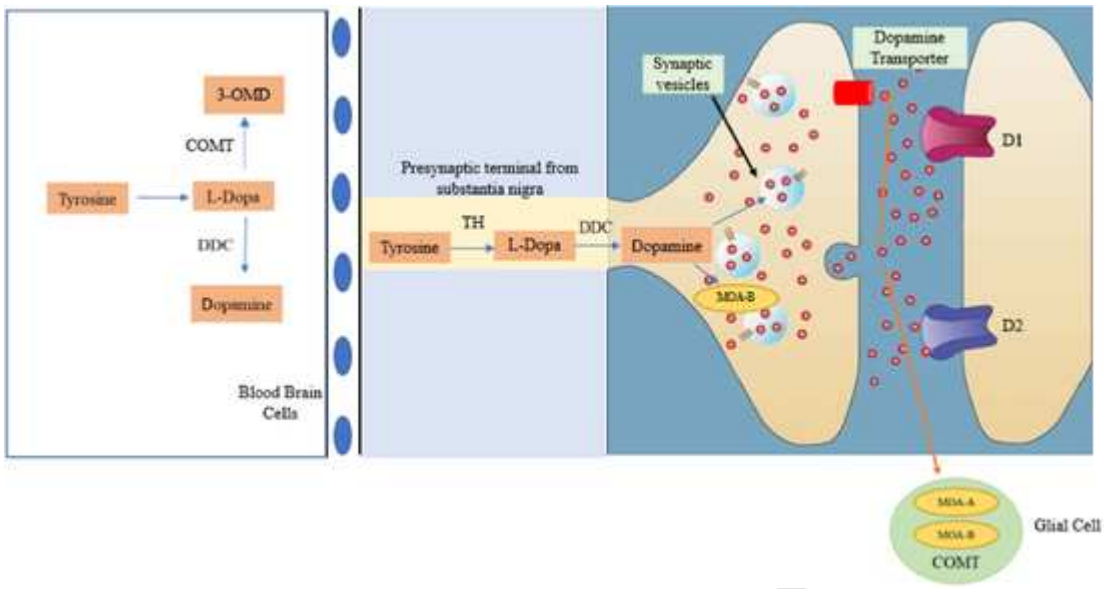

Fig. 8. Pathways of dopamine metabolism.

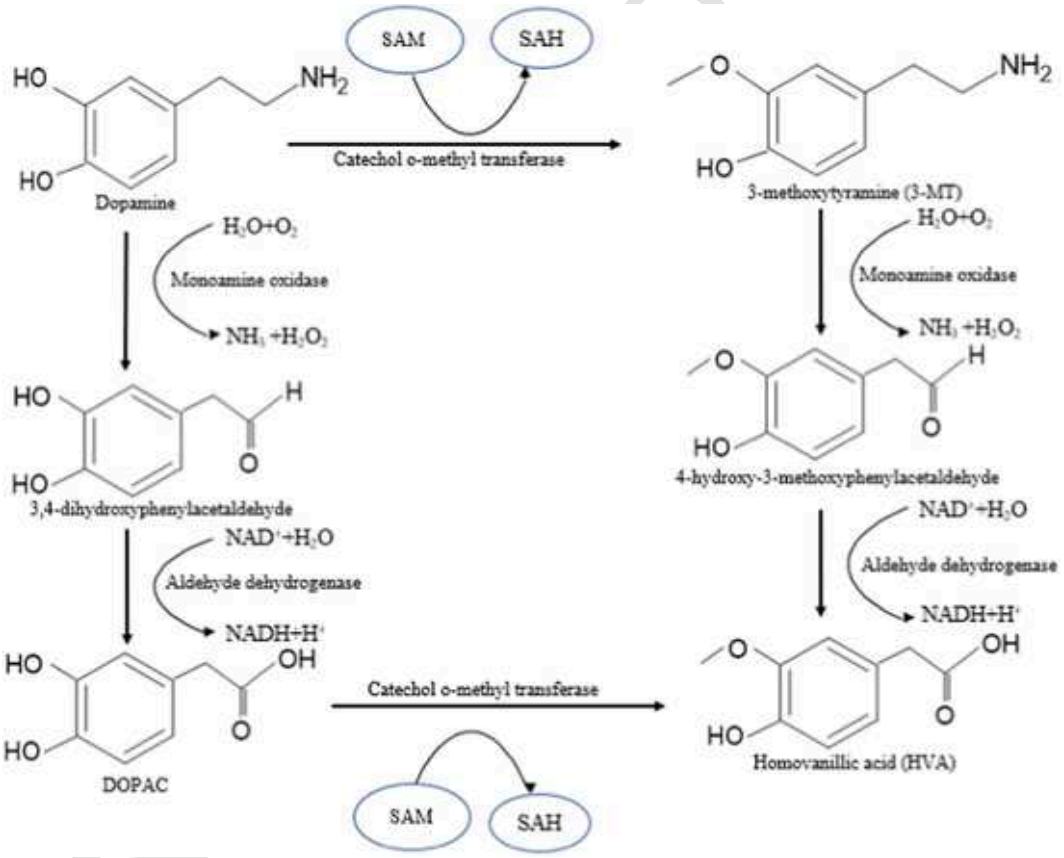

Fig. 9. Metabolism of dopamine to homovanillic acid.

semiquinone. In the second reaction, two dopamine-o-semiquinones are combined and form one molecule of dopamine-o-quinone and one molecule of dopamine. In reaction 3, dopamine-o-semiquinone alternatively reduces oxygen to superoxide and changes into dopamine-o-quinone. In reaction 4, tyrosinase acts on dopamine to oxidize two electrons to dopamine-o-quinone. In reaction 5, at physiological pH, cyclization occurs and dopamine-o-quinone changes to leucoaminochrome. In the last and sixth reaction, leucoaminochrome is autoxidized to form aminochrome [79,80,81].

4.4. Dopamine- -quinone, aminochrome, and 5,6-indolequinone relevance in Parkinson's disease

Three quinones are produced during the oxidation of dopamine to neuromelanin (NM), dopamine-o-quinone, aminochrome, and 5,6-indolequinone. These quinones play roles in the dopaminergic neuron degradation to NM. However, the question is which quinone plays this degradation role? When dopamine is oxidized, the first product of its oxidation is dopamine-o-quinone. But the life of this compound is very

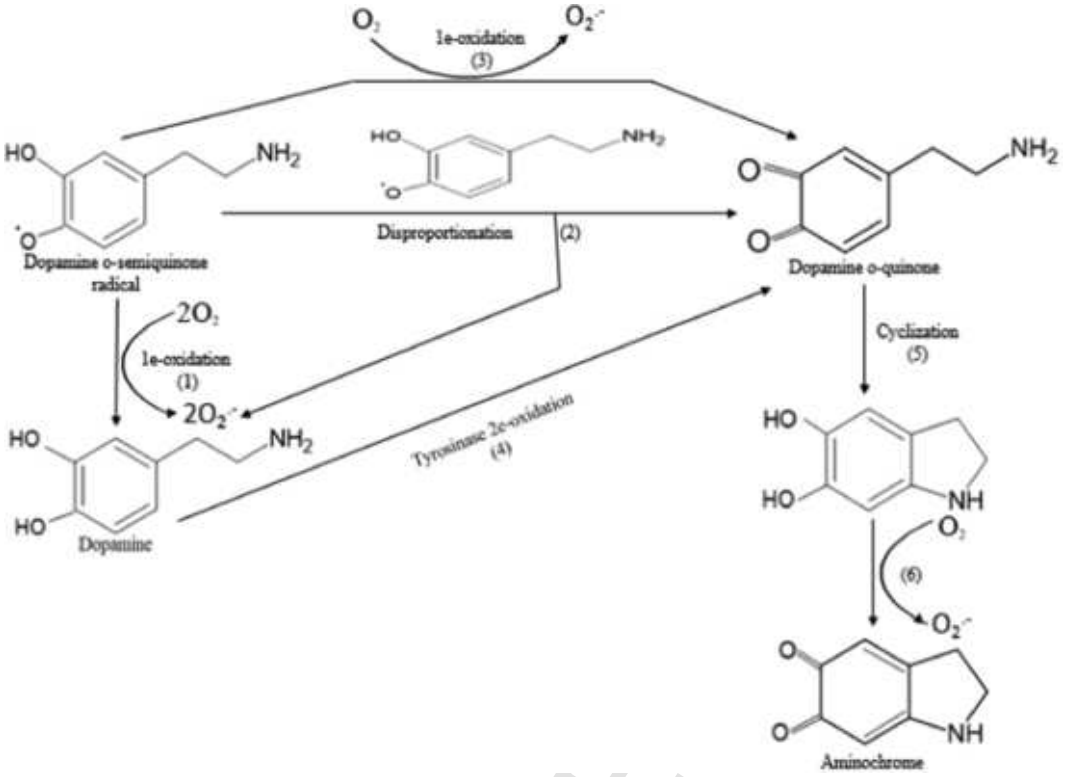

Fig. 10. Oxidation of dopamine to aminochrome.

short, and cyclization occurs at a very high speed (0.1/s). Its short life is due to its stability at a very low pH of less than 2. Sulfhydryl groups such as glutathione have very high reactivity with this quinone. The short life means that it cannot form adducts with alpha-synuclein. Nuclear magnetic resonance (NMR) spectra showed no evidence of the presence of dopamine-o-quinine [82,83].

However, 5-S-glutathionyl-dopamine, which is the conjugated product of dopamine-o-quinone and glutathione, is present in NMR spectra *in vitro*. And the next product of 5-S-glutathionyl-dopamine, which is 5-S-cysteinyl dopamine, is found in the brain and cerebrospinal of PD patients. This reaction has a protective nature, but the question is the same— is this quinone responsible for adduct formation such as alpha-synuclein like the cysteine residue. It is thought that the very rapid cyclization does not allow dopamine-o-quinone to form adducts. The next quinone is 5,6-indolequinone, which is then converted to aminochrome. Four minutes after aminochrome is formed, alpha-synuclein adducts appear. Aminochrome disappears within 20 min, whereas 5,6-dihydroxyindole is present for 40 min. So many possibilities are present here. Maybe the 5,6-dihydroxyindole adducts formed with alpha-synuclein or aminochrome can also form the adduct, and after adduct formation, it may convert back to 5,6-dihydroxyindole. Both quinines are quite unstable, and it is difficult to record their NMR signals [84,85]. Thus, studies are difficult and this topic is still being debated. However, these precursors of NM during dopamine oxidation are very reactive and could play a key role in PD. These quinones are detoxified by cysteine and glutathione residues. Therefore, understanding their role is an important key point in the treatment of PD. Both DT diaphorase (NQO1) and GSTM2 play an important role in inhibiting minochrome neurotoxicity. NQO1 plays a role in dopaminergic neurons and GSTM2 plays a role in astrocytes [86,87].

4.5. The possible effects of dopamine-o-quinone, aminochrome, and 5,6-indole-quinone during dopamine oxidation in dopaminergic neurons

When dopamine is oxidized to NM, it generates dopamine-o-quinone, aminochrome, and 5,6-indolequinone before melanin. These products play both neurotoxic and neuroprotective roles. Both the protective and toxic roles have been examined [88].

Fig. 11 presents all of the reactions in this conversion and describes the toxic and protective roles of these products. These quinines are too unstable to study their roles separately, so we put them in the same pathway [88,89,90].

4.5.1. Protective role

- In reaction 1, after dopamine formation in the cytosol of neurons, dopamine is taken up by VMAT 2 to the monoaminergic vesicles. This prevents dopamine oxidation. This step plays a neuroprotective role.
- In reaction 2, dopamine is oxidized to dopamine-o-quinine.
- In reaction 3, the cyclization of dopamine-o-quinine occurs, and it is converted to aminochrome.
- In reactions 4 and 5, before the formation of NM from aminochrome, there is a rearrangement within the aminochrome molecule, and it is converted to 5,6-indolequinone.
- In reaction 6, two electrons are reduced in aminochrome, and leucoaminochrome is formed by DT-diaphorase.
- This prevents aminochrome from playing a role in neurotoxic reactions [91,92,93].

4.5.2. Neurotoxic role

In the neurotoxic role, dopamine-o-quinone, aminochrome. and 5,6-indolequinone form adducts with alpha-synuclein and generate toxicity within the neuron [94] (Fig. 11).

The following reaction describes the neurotoxic effect of these products:

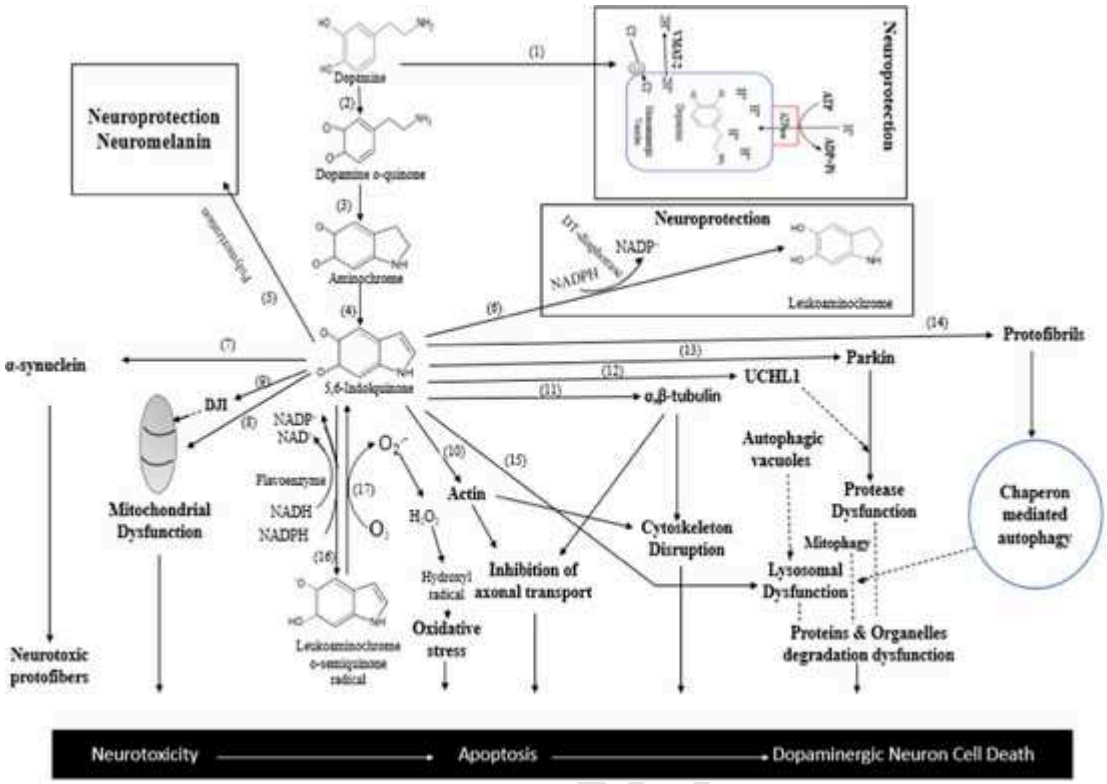

Fig. 11. The possible effects of dopamine-o-quinone, aminochrome, and 5,6-indolequinone during dopamine oxidation in dopaminergic neurons [91].

- In reaction 7, neurotoxic protofibrils are formed when aminochrome and 5,6-indolequinone react with alpha-synuclein [95,96,97].
- In reaction 8, dopamine-o-quinine adducts form by binding to complexes I, III, and V (ATPase of the electron transport chain). Mitochondrial dysfunction occurs from oxidative phosphorylation and isocitrate dehydrogenase during the Krebs cycle [98].
- In reaction 9, when dopamine-o-quinine forms adducts with alpha-synuclein, these adducts lead to the inactivation of DJ-1 protein. This protein is important in the inhibition of oxidative stress when the mitochondrial electrons are reserve. Any defect in DJ-1 protein increases oxidative stress, producing neurotoxicity [99,100,101].
- In reaction 10, some adducts are also formed by the reaction of aminochrome with actin. Mitochondria require the interaction with neuro filaments. However, the formation of these adducts disturbs the mitochondrial transport function to axons and dendrites, which also causes toxicity within the neuron.
- In reaction 11, for axonal transport and the fusion of vacuoles with lysosomes during autophagy, the formation of microtubules is necessary. However, quinines from the adducts with α- and β-tubulin prevent the formation of microtubules. Thus, the autophagy process is disturbed, and toxicity is produced within the cell [102,103].
- In reaction 12, adducts and inactivated UCHL-1 are formed by aminochrome [104,105].
- In reaction 13, adduct formation inactivates the parkin protein, which is a ubiquitin ligase of the proteasome [106].
- Protein and organelle dysfunction occur due to the lysosomal system and ubiquitination.
- In reaction 14, chaperone-mediated autophagy is inhibited by alpha-synuclein protofibrils.
- In reaction 15, toxicity is produced by lysosomal function disturbance caused by the formation of adducts with vacuolar ATPase. This ATPase helps the lysosome to maintain its low pH by generating an H + gradient [87].
- In reaction 16, aminochrome is one-electron reduced and changed to leucoaminochrome-o-semiquinone.
- In reaction 17, the reduced oxygen is autoxidized to superoxide radicals [107,108].
- In reactions 16 and 17, the sources of NADH, NADPH, and O_2 are decreased.

5. Conclusion

As dopamine is a neurotransmitter, its low concentrations in the substantia nigra prevent the transmission of nerve impulses and the brain cannot carry signals in the proper way. Therefore, there is a loss of connection between the brain and other body parts. A loss of dopamine results in the loss of control of body movements. Dopamine is a chemical in the brain whose concentration is directly related to PD. There are five subtypes of dopamine receptors, D1, D2, D3, D4, and D5. These subtypes are further divided into two subclasses of D1-like family receptors (types 1 and 5) and D2-like family receptors (types 2, 3, and 4). The inhibition of prolactin production, movement, behavior, motivation, punishment, learning, reward, cognition, attention, dreaming, working memory, mood, and sleep involve different functions performed by dopamine. Dopamine is formed by four major pathways along with direct and indirect pathways. Dopamine is metabolized into three quinones, but due to their unstable nature, scientists cannot determine which quinone causes the formation of adducts with synuclein. Dopamine is oxidized to three quinines and this form adducts with synuclein, which disturbs the function of synuclein. However, scientists have been unable to identify which quinine forms adducts with synuclein because they are very unstable and disappear a few minutes after production. Nonetheless, it is very important to know which quinine makes these adducts for the treatment of PD. Dopamine cannot pass through the blood–brain barrier so cannot be used directly for the treatment of PD. Pharmacological targets of dopamine and the dopaminergic system should be explored for the treatment of PD. These approaches can be based on the expression and secretion of dopamine as well as the activation of its receptors.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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