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TOXICITY OF LEVODOPA IN PARKINSON DISEASE THERAPY

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ABSTRACT

Parkinson's disease is a universal progressive neurological disease, being a more common neurodegenerative disease in the population between 58 and 69 years old. It is constituted as a disease by the degeneration of the black base substance, where a dopamine is synthesized, associated to the presence of cytoplasmic molecules formed by the accumulation of proteins such as Lewy corpuscles. The choice of treatment depends on the functional deficit and response to the treatment already used. Levodopa (L-Dopa) is the most commonly used antiparkinsonian, as well as the most potent, highest cardiac standard, able to cause all symptoms. However, with the prolonged treatment and the high doses given, it is common for undesirable symptoms to appear and a drastic reduction of the window, so it is very clear to know it. Thus, this work aimed to investigate a disease that occurs in the disease during the most common degenerative disease among the elderly and one is associated with the medications in patients with Parkinson's disease, through a simple, descriptive bibliographic review of the last twenty years.This work was developed as a primordial tool for conducting a long term study.

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INTRODUCTION

One of the most striking facts of this new century is the aging of the world's population. The demographic transition, marked by a reduction in birth and death rates and an increase in life expectancy, led to an increasing volume of chronic and degenerative diseases peculiar to more advanced ages (CARVALHO AND GARCIA, 2003; TANNURE *et al.,* 2010). In Brazil, the more conservative statistics suggest that by 2020 we will be the sixth country in the world in terms of the number of elderly people (CARVALHO AND GARCIA, 2003). These changes reflect in the continuous development of social problems, which, while offering so many facilities for a larger number of people, also cause stress for a large part of the elderly, becoming an unfortunate result for maintaining the health of this population and preservation of their permanence with the family (ALMEIDA, 2005; PERTERNELLA *et al.,* 2009). In view of this, chronic degenerative diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (DH) and Amyotrophic lateral sclerosis (ALS), form a diverse group of progressive diseases and due to the properties they are in the group of pathologies with the greatest devastating effect in medicine, and there is no cure yet discovered by the scientists. They involve the deterioration of brain functioning, resulting from the progressive degeneration and / or death of the neurons, which are the base unit of the nervous system, where they communicate with each other through synapses and are responsible for the propagation of the nerve impulses, causing the loss of capacity acquired (ALMEIDA, 2005; TAVARES *et al.,* 2018). Among the most common degenerative diseases (NDs) in the elderly are PD, considered the second most frequent Neurodegenerative Disease in the population aged 58-69 years, with a significant increase in the incidence in the population above 80 years[6]. It affects all ethnic groups, socioeconomic classes and genders. However, its prevalence and incidence in men is still higher than in women (BRASIL, 2010). PD is one of many forms of parkinsonism, and also the most frequent, accounting for about 75% of cases. Parkinsonism corresponds to a generic term that designates a series of diseases with different causes and that have in common the presence of parkinsonian symptoms. Currently, parkinsonian syndromes can be clinically considered in three major groups: Idiopathic PD; a second group, consisting of a heterogeneous and still incomplete set of DNs whose parkinsonian symptoms constitute only part of the

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clinical picture; and symptomatic or secondary parkinsonism to other defined causes (GUIMARÃES and ALEGRIA, 2004; TEIVE, 2005). Consequently, due to a mutable clinical spectrum and coincidence with multiple neurological conditions of different causes, it is necessary to be sure about the diagnosis of the disease, particularly in the early stages. Diagnostic errors result in delays in treatment or even inappropriate treatments. Currently, neuroimaging tests are revolutionizing the diagnosis of the disease, which can provide the patient with Parkinson's a safe diagnosis, as well as the hope of new therapies, since, as yet, there is no drug that prevents the disease from developing and progressing. Above all, the PD milestone was with the introduction of Levodopa (L-Dopa), which revolutionized the life of the IPD carrier. It has become the most potent treatment among all drugs on the market, capable of both performing a differential diagnosis and reducing the symptoms of the disease. It is the immediate natural dopamine precursor of dopamine, where the amino acid aromatic decarboxylase (AADC) converts it to dopamine (Dopa). The initial euphoria was great, although some problems arose (AZEVEDO AND CARDOSO, 2009). Through the above, the aging of the brazilian population is an irreversible fact, which is expected to accentuate in the near future. The occurrence of disorders and disorders arising from years of active life and stressful behaviors, become almost all chronic neurodegenerative diseases. The need for measures to ensure greater information and dissemination on health aspects will be one of the most relevant points to be debated today. For this reason, the importance of conducting and propagating research that addresses the best way to deal with and treat this population. Thus, it is of fundamental importance to deepen the pharmacological treatment of second-rate disease in the elderly and its main limitations that are manifested in the long term, therefore, the main objective of the present study was to conduct an investigation, from a an expositive expository approach about the Levodopatherapy used in the chronic degenerative disease, more common among the elderly and if it is related to toxic effects in patients with PD. As a result of the general objective, the study aimed at investigating the following aspects related to the theme: the pathophysiology of PD; the usual therapy with Levodopa and its pharmacodynamics; relate the unwanted effects of Levodopa to the patient's dopaminergic receptors; and elucidate possible toxic effects of levodopa by prolonged use.

REVIEW

History of Parkinson's Disease (PD): Parkinson's disease (PD), had the first world description well defined in 1817 in a monograph entitled An Essay on The Shaking Palsy, James Parkinson's "Paralysis Stirring" (1755-1824), physician, member of the Royal College of Surgeons, born in a middle-class family in London, England (ALMEIDA, 2005; AZEVEDO and CARDOSO, 2006). The trial had 66 pages, 5 chapters, 6 illustrative cases, primary symptoms, differential diagnosis and contemplation regarding the origin of the disease and treatment. They were men, between 50 and 72 years old, three were personally examined, two were found casually on the street and evaluated later and one of the cases was not evaluated (BERRIOS, 2016). He defined as a disease of slow evolution evidenced by the presence of trembling involuntary movements, reduction of muscle strength, tendency to submit the torso forward and with gait alteration, which would lead to recurrent falls. Parkinson argued that PD was a different form of paralysis, because regardless of all symptoms, his patients remained with perfect senses and intellect (BERRIOS, 2016 AZEVEDO and CARDOSO, 2006). Although the contribution of the trial on agitating paralysis by Parkinson's was fundamental, the disease only became well known after a few years. Several neurologists reported articles on the disease, however, Charcot played a key role, as he was the one who studied the disease in which new symptoms were discovered and was responsible for divulging it (ALMEIDA, 2005; PAIXÃO, 2013). Jean-Martin Charcot (1825-1893) neurologist and professor, proposed to change the name of Agitating Paralysis to Parkinson's Disease, named after James Parkinson. He distinguished PD from multiple sclerosis (MS) by type of tremor, emphasizing that the tremor of PD would be slow and that of MS would be accelerated, determining the four main signs of the disease (GOETZ *et al.,* 2011). However, other factors may be related to disease, such as environmental neurotoxins, mitochondrial abnormalities, phosphorylative oxidation, increase in free iron levels and oxidative stress (FONSECA *et al.,* 2018). The hypotheses oscillate between two main currents, which are: environmental toxic factors and genetic factors, since it is estimated that 20% of the patients have at least one first-degree relative with PD (STANDAERT *et al.,* 2007; JÚNIOR, 2017). DPI occurs due to the progressive and irreversible death of the dopaminergic neurons of the substantia nigra of the midbrain associated with the presence of cytoplasmic inclusions formed by the Lewy bodies (formed as a cytoprotective response to sequester and degrade excessive levels of potentially toxic abnormal proteins within neuronal cells, which are regions closely related to the motor system that controls muscle activity (RODRIGUES and CAMPOS, 2006).

The diagnosis of PD in its early stages is not always easy. Sometimes the signs and symptoms are hardly characterized and thus confused with other pathologies. The motor symptoms of PD are comprised of four main signs, defined by Charcot: resting tremor, bradykinesia (abnormal slowness of voluntary movements), muscular rigidity and postural instability. However, they only appear when there is neurodegeneration of approximately half the dopaminergic neurons of the midbrain and the loss of 80 to 90% of the dopamine content, which affects not only the symptomatic motor part, but also the cognitive and emotional part of the patient diagnosed (JÚNIOR *et al.,* 2017; NATIONAL PARKINSON FOUNDATION, 2018). Its treatment is only symptomatic, aiming to restore the levels of dopamine in the brain, since no therapeutic option plays the role of the disappearance of neural degeneration. The choice of treatment depends on the functional deficit and the response to the treatment already used, being the pharmacological, obligatory to the patient. Among the classes and pharmacological agents are dopamine precursors, dopamine receptor agonists and dopamine metabolism inhibitors (STANDAERT *et al.,* 2007). In the absence of these, PD progresses in a period of 5 to 10 years, leading to a stiffening stage, in which the patient presents difficulties in self-care, as well as several complications, such as aspiration pneumonia and pulmonary embolism, which can lead to patient to death (STANDAERT *et al.,* 2007). In the literature, the recognition in which L-dopa is the most effective pharmacological resource for the treatment of IPD is unanimous. In theory, all patients with PD will be treated with levodopa. However, the more the cells degenerate, the more difficult the drug replacement of dopamine. They prove this, the patients who in the initial phase respond very well to the treatment, but after five to ten

years, they present severe alterations in the response. That is, they change the parkinsonian symptoms by abnormal involuntary movements. Initiating a pharmacological maneuver difficult to monitor (AZEVEDO, *et al.,* 2009). Moreover, in order for a treatment to achieve its success, it is necessary to carry out a reliable evaluation of the patient to determine his or her true level of commitment, since this is a degenerative and progressive condition, the intervention must be adequate for the patients'needs of the patient. Thus, there are scales that assess the general clinical condition, disability, motor and mental function up to the quality of life of patients, allowing the monitoring of disease progression and the effectiveness of treatments and drugs (CIRNE, 2017). Among these instruments are the Hoehn and Yahr Disability Stages Scale, developed in 1967, which indicates the patient's general condition in a quick and practical way, thus allowing the individual to be classified as to their level of disability and the Unified Scale of Evaluation in DP – UPDRS (ALMEIDA, 2005; European Parkinson's Disease Association, 2018).

Epidemiology

So far, one cannot safely determine the number of people who have Parkinson's. A Global Disease Burden Study of 2015 estimated the prevalence of Parkinson's in about 6.2 million people worldwide, but in reality the number may be considerably higher since many people are not diagnosed (European Parkinson's Disease Association, 2018). The disease is found in all ethnic groups, but when observed geographically, it is possible to observe differences in its prevalence, since it is more common in developed countries, justified in the fact that people live longer. It mainly affects elderly people, in the age group between 58 and 69 years old, with a higher prevalence in males. However, in some rare cases, the onset of the disease may occur earlier, before the age of 40 or even below the age of 21 (Parkinsonism). Studies indicate that the incidence of PD is approximately 10 to 50 new cases per year and its prevalence ranges from 100 to 300 cases per 100,000 inhabitants. However, due to the aging of the population, the number of patients with PD is expected to double by 2030 (ALVES *et al.,* 2005). The PD does not distinguish race, social class or even sex, but in general, only studies of epidemiological evidence of the European, Asian and American population are found in the literature, and epidemiological studies on the disease in the Northeast of Brazil are insufficient (ALVES *et al.,* 2005).

METHODS

This study is a simple bibliographical study, submitted to careful reading and analysis presented in a descriptive way of the last twenty years (1998 to 2018) related to PD and its treatment with Levodopa. To perform this work, Lilacs (Latin American and Caribbean Literature in Health Sciences), Portal of Periodicals CAPES / MEC, Scielo (Scientific Electronic Library Online) and Medline (International Literature in Health Science).The languages searched were Portuguese and English. As descriptors were used the words neurodegenerative diseases, Parkinson's disease, dopamine, side effects and adverse reactions related to medications, pathophysiology and levodopa. The inclusion criteria of articles for the study were: the approach of those who related the use of Levodopa as the main drug for the treatment of Parkinson's with the adverse effects caused by prolonged use of Levodopa, as well as those that responded to the questions raised by the work. Studies that failed to provide answers to the questions proposed by the study were excluded.

DISCUSSION

Pathophysiology of parkinson's disease: PD is a chronic progressive degenerative disease of the Central Nervous System (CNS) that affects a region of the brain known as the "Extrapyramidal System", formed by the thalamus, cerebellum and basal ganglia (special centers that are in charge of establishing intercommunications and connecting the various brain areas). This system corresponds to a set of anatomical structures involved in motor control, particularly with regard to the planning and coordination of complex motor activities (JÚNIOR *et al.,* 2006). The basal ganglia are clusters of neuronal bodies, the main components of which are the caudate nucleus, the putamen, the pale globe, the subthalamic nucleus, and the substantia nigra. The caudate nucleus, the putamen and the pale globe form the striatum, and are closely related to each other, participating in the control of posture and movement. The basal nuclei do not have a direct connection to the spinal motor neurons and, therefore, do not directly control the individual movements of the muscles, with this, the role of dopamine arises (STANDAERT and GALANTER, 2009). In DP, a selective loss of dopaminergic neurons occurs in the compact part of the substantia nigra (SN), which causes inability to maintain desired amplitude and sequence of the movements necessary for gait. Dopamine produced in the substantia nigra functions as an inhibitory neurotransmitter in the striatum (Figure 1).

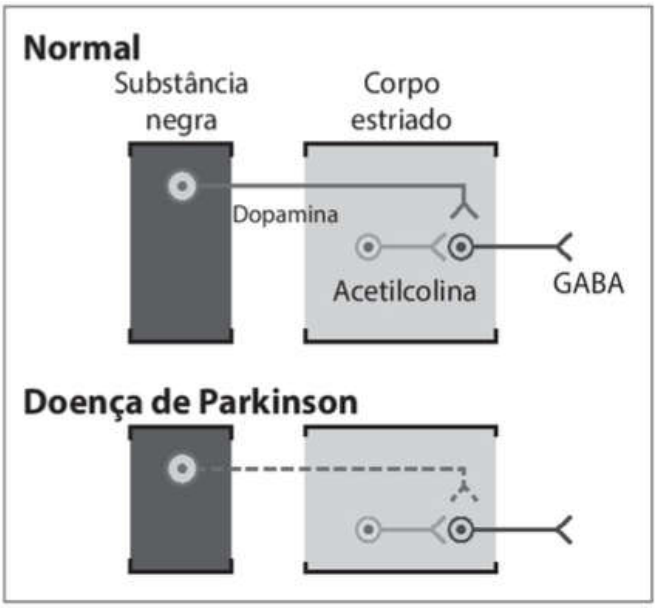

Figure 1. Changes in neuronal circuitry in Parkinson's disease

When a movement is initiated by the cerebral cortex, the impulses are transmitted to the striatum, being able to follow two paths. When movement is desired, the neurons of the striatum increase the activity of thalamic neurons and the cerebral cortex, facilitating the execution of movements (Figure 2). However, if the movement is undesired, there is activation of the SN neurons, which inhibit the thalamic and cortical cells, inhibiting the movements (RODRIGUES AND CAMPOS, 2006; FOX, 2007). The neurons located in the mesencephalon that make up the NS, contain the dark pigment melanin (neuromelanin), which is produced along with dopamine. As the disease progresses and the neurons

degenerate, there is a depigmentation along with the development of included cytoplasmic bodies, which are the so-called Lewys bodies (ALMEIDA 2005). The cause of degeneration of dopaminergic neurons is still unclear, but the combination of genetic and environmental factors seems to be related, such as certain neurological infections and medications, resulting in secondary forms of the disease. Other neurotransmitters are also involved in the neuropathology of this disease. Symptoms such as stiffness and tremor involve neurochemical disturbances of the catecholamines acetylcholine, noradrenaline and serotonin. Any disease that includes striatal dopamine deficiency or direct striatal damage may lead to the syndrome known as Parkinsonism (STANDAERT AND YOUNG, 2007).

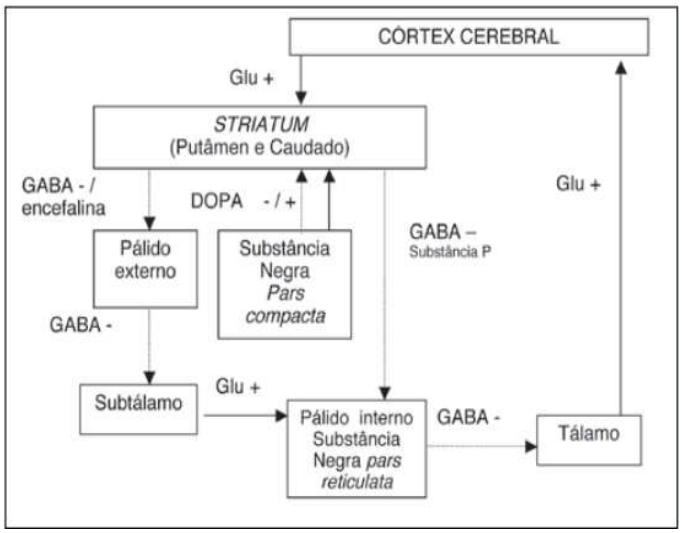

Figure 2. Normal circuit of the basal ganglia with the main neurotransmitters involved. Full arrows correspond to excitatory stimuli; arrows dotted, inhibitory. Glu = glutamate; GABA = gamma-aminobutyric acid; DOPA = dopamine. Direct: Striatum and inner pale. Via Indirect: Striatum, pale external, subthalamus and inner pale.

Dopamine

Dopamine belongs to the catecholamine family of neurotransmitters, synthesized from tyrosine in the cytoplasm of the neuron, which is mostly obtained through diet. CNS catecholamines modulate the function of neurotransmission from point to point and directly affect mood, attention and emotion. According to Figure 3, the first step in DA synthesis is the conversion of tyrosine into L-DOPA. This reaction is catalyzed by the enzyme tyrosine hydroxylase (TH), a ferro-enzyme composed of four identical subunits. In addition to Fe2+, TH also requires the tetrahydrobiopterin cofactor, which is oxidized to dihydrobiopterin during the reaction, followed by the conversion of L-DOPA into Dopamine by the enzymatic amino acid decarboxylase (AADC), which is abundant in the brain (BERTOLUCCI *et al.,* 2016; SAITO, 2011).The release of stored dopamine occurs by exocytosis, being transported out of the synaptic cleft by the selective dopamine transporter (DAT) coupled to Na+ and retransported by the VMAT while another part is degraded by the sequential actions of monoamine oxidase (MAO) and catechol -O-methyl transferase (COMT), giving rise to two metabolic products, 3,4-dihydroxyphenylacetic acid (DOPAC) and 3-methoxy-4-hydroxyphenylacetic acid (HVA) (STANDAERT and YOUNG, 2007; FRANCO, 2016).

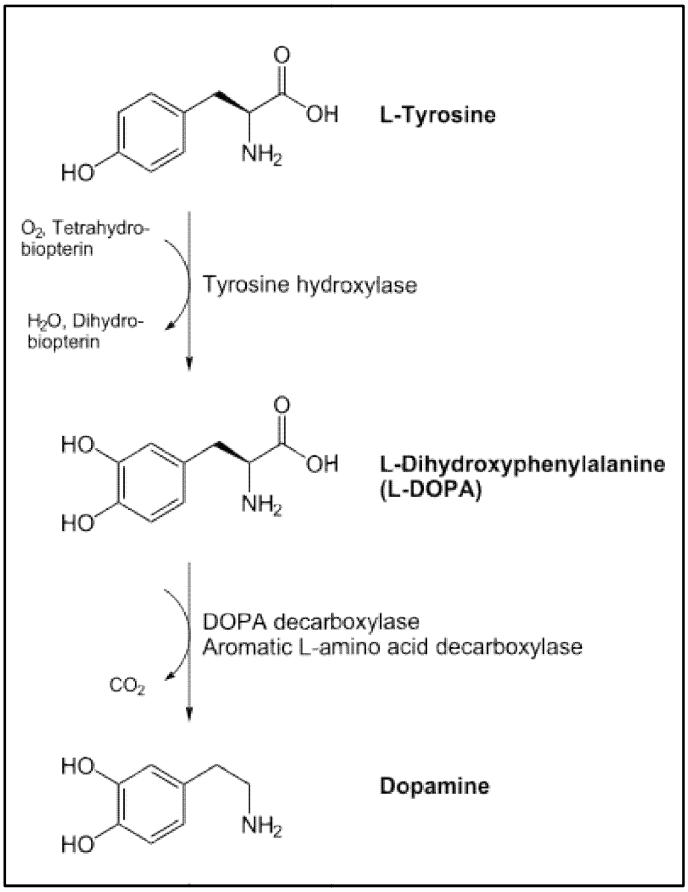

Figure 3. Synthesis of Dopamine

Dopamine receptors

Dopamine receptors are members of the G-protein coupled receptor family of proteins. There are 5 different types of dopamine receptors in the brain, D1, D2, D3, D4 and D5, but, as far as Parkinson's disease is concerned, most important receptors in the treatment are D1 and mainly D2 because they are located in the nigrostriatal pathway (Figure 4), responsible for motor control. D1 stimulant and D2 inhibitor of cyclic AMP synthesis (3':5'-adenosine monophosphate-cyclic) (STANDAERT and YOUNG, 2007; STANDAERT *et al.,* 2009; FRANCO, 2016).

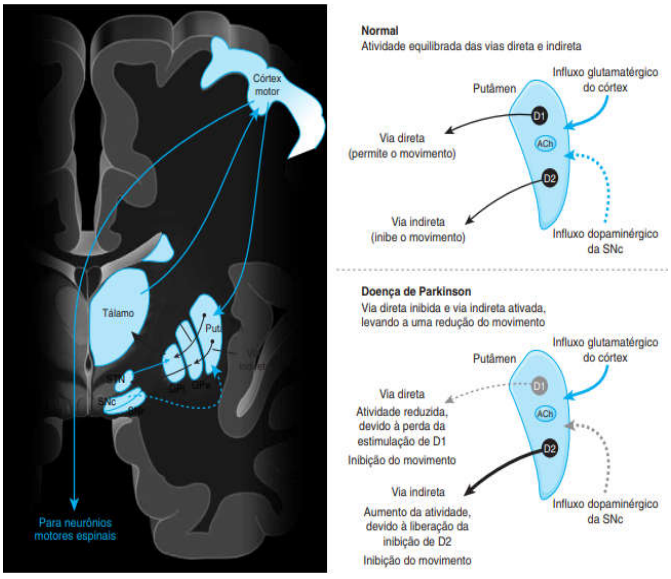

Figure 4. Effect of Parkinson's disease on the dopaminergic pathways

Pharmacological treatment of Parkinson's disease

All the treatments for PD to date are symptomatic, that is, they only treat the symptoms and do not alter the degenerative process of the disease. DA replacement, which is the main reason for the development of the disease, is not adequate for the treatment of PD because it is unable to cross the blood-brain barrier (BHE), a highly selective permeability structure that protects the Central Nervous System potentially neurotoxic substances (SAITO, 2011). In view of this, interventions revolve around the restoration of dopamine levels in the brain. Among the pharmacological treatments, there are the precursor classes of DA, agonists of DA receptors and inhibitors of AD degradation (AZEVEDO and CARDOSO, 2009).

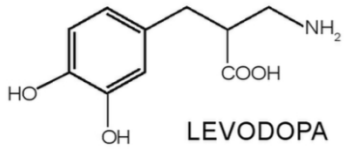

Figure 5. Levodopa

Levodopa

In the 1960s, the first successful treatment for PD emerged. The incorporation of Levodopa or L-dopa (3,4-dihydroxy L-phenylalanine (Figure 5) by George Cotzias (1918-1977) was the major therapeutic advance for the treatment of IPD. It forms as an intermediate in dopamine biosynthesis, used as a pro-drug to increase dopamine levels in the brain, since it has the ability to cross the BBB, whereas dopamine alone, cannot. Its therapeutic as well as adverse effects result from its decarboxylation in dopamine (FERRAZ and BORGES, 2002). Oral levodopa is highly metabolized in peripheral tissues and in the gastrointestinal tract (GIT) by the aromatic 1-amino acid decarboxylase (AADC), catechol-O-methyltransferase (COMT) and monoamine oxidase (MAOA), as shown in Figure 6. This metabolic process decreases the bioavailability of levodopa able to reach BBB for its expected CNS effect. When given alone, only 1% of the unchanged drug is able to reach the cerebral circulation. Therefore, levodopa is given in combination with enzyme inhibitors such as carbidopa and benserazide (AADC inhibitors) and tolcapone and entacapone (COMT inhibitors). This association helps to reduce the conversion of levodopa to dopamine, reducing adverse reactions and increasing the amount of plasma levodopa available to cross BHE (STANDAERT and YOUNG, 2007; FRANCO, 2016; FERREIRA, 2010; SOARES, 2017). Once within the Central Nervous System (CNS), levodopa is metabolized to dopamine through the action of the enzyme L-amino acid aromatic decarboxylase (AADC). Its storage occurs in the presynaptic vesicles and then released to the postsynaptic receptors (STANDAERT AND GALANTER, 2009). Despite this, even after more than 25 years of successful use of levodopa in the disease, it is not known exactly how the conversion of the striatum occurs. The mechanism hypothesis is the uptake of levodopa by the surviving nigrostriatal synaptic terminals (SOARES, 2017). Its absorption depends on the rate of gastric emptying and its pH, so it is found so diffusely in the literature, the follow-up of the PD patient in relation to the association of a protein-rich diet with the administration of Levodopa, since the amino acids and the drug compete for binding sites on the carrier, decreasing the absorption thereof. Levodopa is transported into the brain by the same active transport systems and in general, maximum plasma concentrations are found after 1 to 2 hours of oral administration; with a mean plasma half-life of 1 to 3 hours (STANDAERT and YOUNG, 2007; STANDAERT *et al.,* 2009; FRANCO, 2016; FERREIRA, 2010; SOARES, 2017). At the onset of disease progression, levodopa therapy may have a complete effect on all signs and symptoms of IPD, leading to a degree of improvement of almost complete tremor, stiffness and bradykinesia. However, after a period of satisfactory response to levodopa, patients usually begin to develop complications as a result of this drug treatment. It is believed that such complications reach 50% of parkinsonians with five years of levodopa use (PROTÓGENES, 2010). Continuous stimulation of dopaminergic receptors, due to the loss of dopamine storage capacity due to the death of neurons from the substantia nigra, may be directly related to the central issue of these complications in the central nervous system. Therefore, the presence of unwanted symptoms such as sedation, psychiatric symptoms, motor fluctuations and dyskinesias (involuntary repetitive movements) may be inherent to the patient being treated. The literature reports that dyskinesias arise from the association of two factors: the intensity of dopaminergic damage and the chronic administration of levodopa (SAITO, 2011).

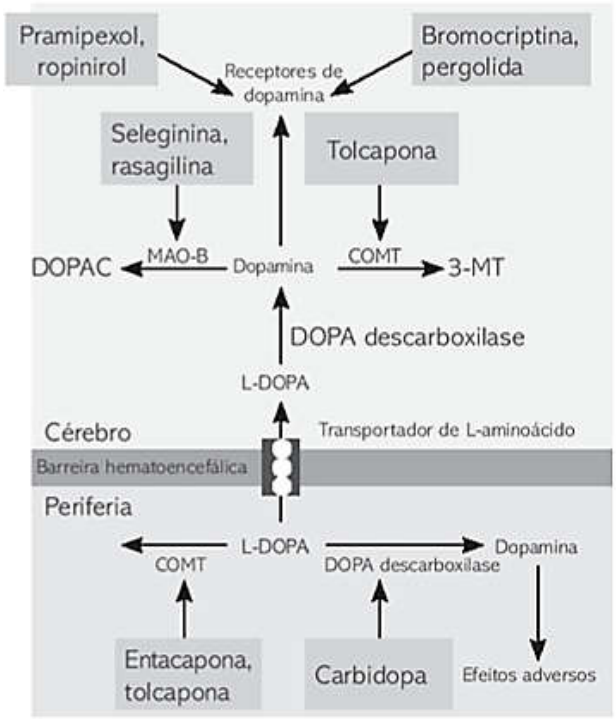

Figure 6. Metabolization of Levodopa

Other phenomena are also related to Levodopa users. Among them, there is the existence of the "wearing off" phenomenon characterized by a shortening of the duration of the motor effect of levodopa, causing the patient to have the benefit of the medication (on state) for two or three hours , needing to receive a new dose to return to the mobility. When the phenomenon sets in, there is a natural tendency to add new doses of levodopa, but with this measure, the patient ends up progressing to a clinical situation, where the dosage of levodopa becomes infeasible in a short time. Among the factors that may contribute to shortening the duration of the effect of levodopa are: slow gastric emptying, irregular absorption of levodopa in the gastrointestinal tract and passage through the blood-brain barrier (STANDAERT *et al.,* 2007).

There is also an on-off phenomenon where there is a rapid change in the patient's state of mobility without any relation to the time taken to administer levodopa. Some patients may be hours off, ie completely akinetic, despite taking consecutive doses of levodopa. Because they are unpredictable, these fluctuations are extremely disabling. This type of complication is the most difficult to control (SAITO, 2011).

Conclusion

However, the questioning becomes unavoidable in relation to the use of levodopa in the patient with Parkinson's disease. However, there is still no convincing evidence to explain whether levodopa actually produces free radicals (toxic effects) as a result of dopamine metabolism that directly contributes to the death of nigrostriatal neurons and whether this factor can accelerate the degeneration process of disease.

The fact that it is indeed proven is that the treatment of PD during the first years of illness produces important symptomatic improvement in most patients. However, as the pathological process progresses, difficulties widen, causing increasing functional disability. This therapeutic limitation is reflected in the observation that, even after the introduction of levodopa, the life expectancy of patients with PD is lower than that of the general population. There is much controversy about whether or not to initiate levodopa in Parkinson's patients, since its side effects and complications of levodopa are a significant source of disability and carrier morbidity. In these circumstances, as a consequence of this unresolved controversy, it is necessary to use non-pharmacological measures and other classes of therapeutic drugs, which will help to improve the quality of life of patients with idiopathic Parkinson's disease.

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