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INTERACTIONS BETWEEN STRIATAL DOPAMINE AND ADENOSINE RECEPTORS: EFFECTS OF AMINOPHYLLINE ON A PHARMACOLOGICAL MODEL OF PARKINSON'S DISEASE

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ABSTRACT

Parkinson's disease is primarily an extrapyramidal motor function disorder caused by severe degeneration of dopaminergic neurons in the substantia nigra. Current treatment for Parkinson's disease is based on dopaminergic therapy to reverse the effects of striatal dopamine depletion induced by nigro-striatal pathway destruction. The study of new therapies for Parkinson's disease focuses on non-dopaminergic systems inside the basal nuclei that go beyond injured nigrostriatal pathways. Several agents with therapeutic potential have been described, including agents acting on glutamatergic receptors, cannabinoids, opioids, α2-adrenergic receptors and nicotinic and muscarinic cholinergic receptors.The experimental evidencesuggests that the central stimulating properties performed by methylxanthines are neuroprotective and demonstrate beneficial therapeutic effects in the treatment of PD. These results corroborate the hypothesis of a strong interaction between adenosine and dopamine receptors in the striatal middle spinous neurons, playing opposite roles.

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INTRODUCTION

Parkinson's disease (PD) is a chronic degenerative disease of the central nervous system (CNS), with slow and progressive evolution and characterized by symptoms such as bradykinesia, muscle stiffness, tremor at rest, among other motor and non-motor signs (Nasrolahi*et al*., 2019). PD is the main movement disorder found in the elderly population and the second most common neurodegenerative disorder worldwide, second only to Alzheimer's disease (Poewe and Mahlknecht, 2009; Taura *et. al.*, 2018). It is estimated that this disorder can affect about 2% to 3% of the world's population over 65 years, representing up to 2/3 of the patients attending major movement disorder centers worldwide (Poewe *et al.,* 2017). The prevalence of the disease varies between 100 and 200 patients per 100,000 people and with an annual incidence of 15 cases per 100,000 people. Thus, given the increasing occurrence of the disease, prevalence and incidence estimates can be exceeded with the increasing population aging and rising average life expectancy of the world population(Tysnes and Storstein, 2017; Nasrolahi *et al*., 2019). Thus, PD is close to overcome cancer cases as the leading cause of death in the elderly population (Poewe *et al.,* 2017). Literature has reported that PD is a disease that in most cases has an idiopathic cause; however, some etiological hypotheses identify a genetic origin in 5-10% of the patients. In addition, environmental risks may also be associated with the onset of the disease in some cases (Savica *et al*., 2016a). Mortality rates are approximately 3 times higher than those of the general population, highlighting its severity (Larsson *et al*., 2018). Pathophysiologically, PD is characterized by the progressive degeneration of various brain structures, especially the nuclei of the base (NB), especially the substantia nigra, compact part (SNc), causing the death of dopaminergic neurons, compromising the nigro-striatal dopaminergic pathways. This degeneration generates deficits in the facilitation of voluntary movements of chronic and progressive form, determined by the decrease of dopaminergic neurotransmission in the striated body, especially in the

putame (Less *et al*., 2009). In addition, PD is strongly characterized as multiple monoaminergic dysfunction, including, beyond to deficits in dopaminergic systems, decline in other systems such as cholinergic, serotonergic and noradrenergic ones, which may be associated with cognitive impairment and depression that may also accompany the DP throughout its evolution (Jenner, 2014; Teive, 2005). In PD, non-necrotic cells exhibit cytoplasmic inclusions called Lewy bodies formed by the protein accumulation of α-synuclein in dopaminergic neurons of SNc. This is a histological feature of the disease (Tysnes and Storstein, 2017). Characteristic symptoms are rest tremor, muscle stiffness, and akinesia or bradykinesia. However, over the years, studies have evolved, showing that PD symptoms are broad and go beyond motor changes (Postuma *et al.,* 2015a; Pinto *et al*., 2019; Elkouzi *et al.,* 2019).

MATERIAL AND METHODS

This article is a narrative review of the literature on Parkinson's disease and the prospects for use of drugs with substances derived from the methylxanthine group, especially caffeine and theophylline. Narrative reviews provide a broad overview of current knowledge about a topic. These studies are characterized by comprehensive publications, appropriate to expose and discuss the development of a particular subject, from a theoretical or contextual point of view. Narrative reviews are basically the analysis of literature published in books, printed and / or electronic journal articles in the author's interpretation and personal critical analysis. Such category of articles have a fundamental role for continuing education, as they allow the reader to acquire and update knowledge about a specific theme in a short time (Bernardo *et al.,* 2004). The subject was investigated in books on neurology and neuropathology and journals published in the Virtual Health Library (VHL), PubMed electronic databases, totaling 116 articles. The following standardized descriptors were used: Parkinson's disease; Dopaminergic receptors; Adenosinergic receptors; Catalepsy; Basal Nuclei; Methylxanthines. Inclusion criteria were: (1) Research articles, (2) review articles that conducted experiments on PD model animals and evaluated catalepsy and treated the animals with drugs from the MTX group. The articles were read intotum in order to categorize them and then conduct their critical analysis.

DISCUSSION

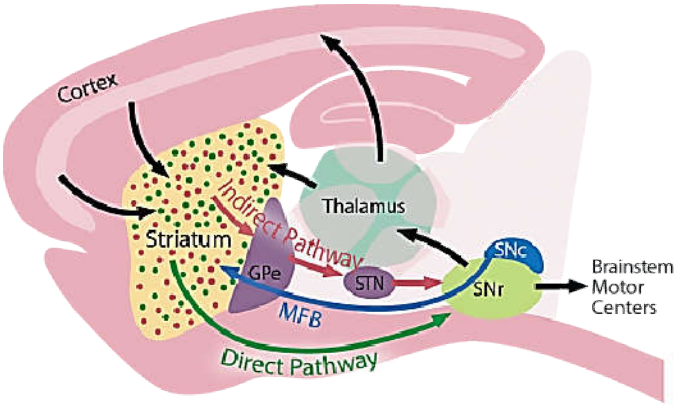
Basal Nuclei: NBs are a group of subcortical nuclei involved in the planning and initiation of movements. These nuclei are organized anatomically and functionally into parallel circuits that process different types of information. NBs are located in the brain and midbrain and are divided into: (a) input nuclei, which receive information from the cortex and thalamus, consisting of caudate, putamen, and accumbens nuclei; (b) output nuclei, which send NB information to the thalamus, constituting the internal pale globe (GPi) and the cross-linked substantia nigra (SNr); and (c) intrinsic nuclei, also known as neostriates, composed by the division of the external pale globe (GPe), the subtalamic nucleus (STN) and the compact substantia nigra (SNc) (Armentero *et al.,* 2011). The neostriatum is formed by a single nucleus in rodents, but in upper vertebrates, it is divided by the inner capsule in the caudate nucleus and putamen. GP, as mentioned, consists of two main parts, the outer segment, GPe and the inner segment GPi. The outer segment is simply called GP in rodents and the inner segment is equivalent (in terms of inputs and outputs) to the entopeduncular nucleus (EP) in rodents (Tepper *et al.,* 2007). The NB composition occurs through the interconnection of several nuclei and these nerve structures are responsible for adjusting the activities in the CNS descending tracts, despite the lack of direct connections between these basal nuclei and the lower motor neurons, their role is paramount for maintaining motor function homeostasis. Regarding motricity, these nuclei act on the regulation of muscle contraction and strength, the movements of various joints and the sequences of movements. Some of these nuclei are anatomically close and therefore have common names: the pale globe and the putamen form the lenticular nucleus and the caudate and putamen together form the striatum (Kandel *et al.,* 2014).

Substantia Nigra: The substantia nigra (SN) is a nucleus located in the midbrain, and characterized macroscopically by the dark staining of its cells, where neurons are pigmented by neuromelanin (Van Domburg and Ten Donkelaar, 1991). In the human brain, an anatomical subdivision of the nigral complex based on studies that have marked dopaminergic cells has been demonstrated (Damier *et al*., 1999). The SN is divided into two subnuclei: the compact part and the reticular part. These two parts of SN share similar inputs, but have different outputs and are composed of neurochemically distinct neuron types. These divisions are also referred to as the NB dorsal and ventral portion; The ventral division consists of the nucleus accumbens, the pale ventral globe (which is probably equivalente to the ventral part of the GPi) and the medial portion of the STN and SN. NB dorsal division is mainly associated with motor and associative functions, while the ventral division is more related to limbic functions (Tepper *et al.,* 2007). The vast majority of neurons in NB are GABA projection, about 98.86%. In the neostriatum, both segments of GP and SNr are also mainly composed of projecting GABAergic neurons, about 95% of neurons in the rodent neostryte (and 75-80% in primates). While the STN contains glutamatergic projecting neurons, the SNc is composed almost exclusively of dopaminergic projecting neurons. In addition, the neostriated also encompasses, almost mostly (except for cholinergic interneurons), well-defined populations of GABAergic interneurons. Thus, it is natural that each of these nuclei express high levels of pre and postsynaptic GABAA and GABAB receptors (Tepper *et al*., 2007). Thus, cholinergic actions inhibit striatal cells of the direct pathway and excite striatal cells of the indirect pathway. Therefore, the effects of acetylcholine are opposed to the effects of dopamine on direct and indirect pathways by inhibiting motor activity.

The SN compact part provides dopamine essential for the function of the splined nucleus. Dopamine acts primarily as a neuromodulator in the neostriatum and is important in modulating the voltage-dependent channels for sodium, potassium and calcium ions in the medium spinous neurons and cholinergic interneurons. This neuromodulation leads to complex and state-dependent changes in neuronal excitability in the neostriatal region (Surmeier, 2006). Dopamine also acts to modulate GABA presynaptic release in the SN. With dopamine production in the compact part of SN the motor cortex activity increases by dopamine binding to two different types of dopaminergic receptors, D_1 and D_2, in the NB circuit. Dopamine binding to D_1 receptors facilitates direct pathway activity, while dopamine binding to D_2 receptors inhibits indirect pathway activity. In other words, the direct pathway

(which increases motor activity) is excited by dopamine, while the indirect pathway (which decreases motor activity) is inhibited. Both effects lead to increased motor activity (Kandel *et al.,* 2014).

Parkinson's Disease: The most common hypokinetic motor disorder of NB is Parkinson's disease, characterized by (1) muscle stiffness that is present in all muscle groups, both flexors and extensors, which is usually accompanied by sudden joint movements; (2) festal gait due to loss of postural reflexes that result in balance problems and may manifest with an unstable, bent posture and a shuffling walk with small steps, followed by the need for faster steps to maintain the balance; (3) rhythmic muscle tremor in PD patients is a static or resting tremor, which refers to involuntary 4-5 Hz movements when the limb is kept at rest but disappears during a voluntary movement; (4) facial hypomimics with mask-like facial expression that is associated with hypokinesia; (5) speech disorders such as dysarthria, aphonia. However, nonmotor symptoms have also been described, including hyposmia, sleeping disorders, gastrointestinal symptoms, urinary incontinence, bradyphrenia, depression and cognitive decline (Nasrolahi *et al*., 2019). PD is a central biochemical pathology, resulting in a progressive neurological disorder of extrapyramidal motor function caused by severe degeneration of SNc dopaminergic neurons. Neuronal death is due to damage to complex I of the electron transfer system; ATP depletion as a result of blockade of mitochondrial oxidation and; changes in calcium ion homeostasis. Decreased dopaminergic neurotransmission leads to degeneration of the striated nucleus and loss of dopamine receptors (Rowland, 2007). Deficiencies caused by dopamine depletion most commonly include motor symptoms which are usually signs used to diagnose PD (Fang *et al*., 2006; Toriumi *et al*., 2009). However, a large body of evidence suggests that this is only one aspect of a multifaceted disorder. About 60% of people with PD also have non-motor symptoms, such as psychiatric disorders and about 40% of them have anxiety and / or depression disorders. These symptoms appear after the loss of at least 80% of dopaminergic neurons in CNS, thus impairing the patient's ability to perform daily tasks. As the disease progresses, comorbidities with nonmotor symptoms manifest themselves (Branchi *et al.,* 2010).



Source:http://nelsonlab.ucsf.edu/publications/publications

Figure 1. Dopaminergic neurons of the substantia nigra compact part, throwing axonal projections to the striated nucleus

Pharmacological treatment of Parkinson's disease: Hornykiewicz's extensive, accurate and pioneering work brought the proposal for levodopa-based (L-DOPA) pharmacological therapies. L-DOPA is a dopamine precursor that remains one of the major therapeutic tools for PD patients (Hornykiewicz, 1973; Hornykiewicz, 2006). Although L-DOPA is a highly effective drug in treating the early stages of the disease, motor complications (on-off, dyskinesia or dystonia) appear in> 50% of patients after 5 to 10 years of continuous administration (Scottish Intercollegiate Guidelines, 2016). L-DOPA induced dyskinesias (LID) associated with long-term treatment may manifest in the form of choreiform movements, dystonia, athetosis, tics and myoclonus. As soon as they appear, dyskinesias usually affect the orobucolingual muscles and may not have a clear relationship with the administration of several daily doses of L-DOPA. With disease and treatment progression, dyskinesias may become more severe and affect other body regions (Zhang *et al.,* 2013). In addition, all currently used therapies treat symptoms and do not significantly modify the disease progression (Munhoz *et al.,* 2015). As a consequence, there is a need for the development of new pharmacological manipulations for the PD treatment. In addition, the introduction of dopaminergic drugs is associated with acute side effects such as nausea, vomiting, hypotension, hallucination, and insomnia (Munhoz *et al.,* 2015). Dopaminergic agonists (pramipexole, ropinirole and rotigotine) are less effective than L-DOPA, but show fewer motor adverse effects (Tarsy, 2016). Finally, MAO-B inhibitors (selegiline and rasagiline) prevent dopamine metabolism in the CNS and are generally used as adjuncts to L-DOPA treatment to improve motor symptoms (Infac, 2010). Undesirable side effects of currently prescribed drugs show that new and alternative therapies are essential to improve the people's quality of life suffering from this disease. Mechanisms aimed at the protection of nigral neurons are also needed.

Since James Parkinson characterized the disease in 1817, important advances have been made in understanding the etiology, pathophysiology, and prognosis of PD, which has led to the development of new highly effective pharmacological therapies for PD (Smith *et al.,* 2012). Thus, it is important that the new manipulations produce agents with anti-Parkinsonian action at all stages of the disease, without losing the drug efficacy and preventing the appearance of side effects such as dyskinesias. Several agents that demonstrate therapeutic potential have been described, including agents that act on adenosynergic, glutamatergic receptors, cannabinoids, opioids, α2-adrenergic receptors, and nicotinic and muscarinic cholinergic receptors (Jenner, 2003). Given the knowledge that other pathways are also affected in PD, it is important that studies of new pharmacological manipulations focus on the non-dopaminergic systems in the basal nuclei, going beyond the injured nigrostriatal pathways.

Stimulating effects of methylxanthines and their benefits in neurodegenerative diseases: Methylxanthines (MTXs) are substances arising from purines, derived from xanthine methylates. MTXs are the main constituent of many widely consumed beverages and foods worldwide, handcrafted or industrially prepared, such as coffee, tea, yerba mate, cola drinks or guarana, non-alcoholic stimulants (known as energy drinks) and cocoa. While caffeine is present at relatively high concentrations in coffee and tea, several other purine metabolites are also present in smaller amounts including theobromine, theophylline and paraxanthine. On the other hand, theobromine and theophylline are present in high concentrations in cocoa (Camandola *et al.,* 2017).

In 1902, the chemist Emil Fischer received the Nobel Prize for his work on purine and sugar metabolism, including the discovery that caffeine is a purinergic component. Indeed, during the century following Fischer's discovery, studies on the effects of caffeine on the nervous system established the psychostimulatory potential of caffeine by elucidating its cellular and molecular mechanisms of action on nerve cells (Kunz, 2002). For several centuries, tea and coffee were the most consumed beverages in the world, and cola drinks are among the first prescribed painkillers when pharmacological treatments were virtually nonexistent (Franco *et al*., 2013; Oñatibia *et al.,* 2016). The earliest evidence of tea and coffee consumption dates from the fifteenth century in monasteries, where monks used coffee as a stimulant to stay awake to perform their evening prayers. The revitalizing properties of the drink soon became known in other countries, notably the Arab countries and the Ottoman Empire, where Venetian traders began introducing *caffe*, from the Turkish word *kahveh*, in Italy around 1570 (Dicum and Luttinger, 1999). Currently, data from the International Coffee Organization (ICO) report pointed to world consumption of about 165.18 million bags of coffee (approximately 16.518 billion liters) in 2018. According to ICO forecasts, Brazil will continue to be the leader production, and it is estimated to be 58.5 million bags in the crop year (April-March) 2019/20 (ICO 2018).

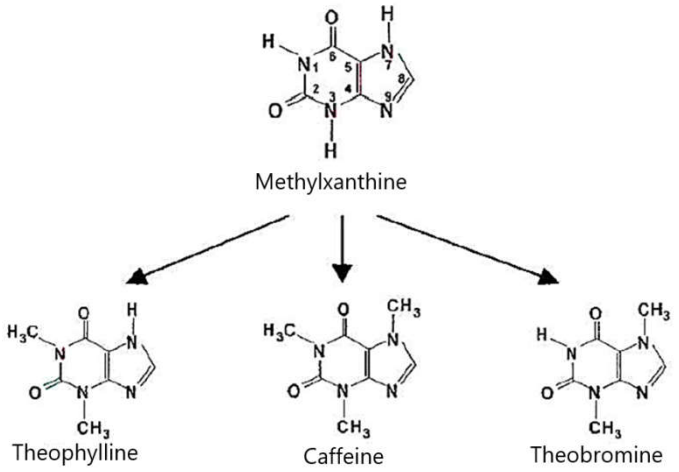
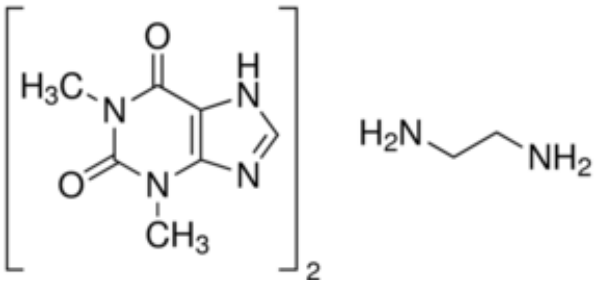


Figure 2. Structure of methylxanthines (Source: Sigma Aldrich)

Regarding the scientific study of MTX group substances such as caffeine, theobromine, theophylline and paraxanthin, solid epidemiological data show that their consumption can prevent serious diseases such as PD, Alzheimer's disease (AD) and diabetes mellitus type II (DM2), classifying these compounds as disease prevention agents agents (Franco *et al*., 2013; Oñatibia *et al*., 2016). The neurodegeneration process is characterized by anatomical, structural damage and physiological changes that lead to neural cell dysfunction and premature neuronal death. In general, clinical practice states that neurodegeneration is attributed as the source of any pathology that exhibits premature neurological symptoms in the absence of cardiovascular injury or events. Neurodegeneration can occur in peripheral and central nerves and encompasses more than 100 distinct diseases. Despite their complex etiology and diverse pathophysiology, these diseases may have common features, such as protein aggregate deposition, inflammation, motor disabilities, and cognitive deficits (Przedborski *et al.,* 2003; Kovacs, 2016). Mammalian studies have concluded that MTXs act through a variety of different molecular mechanisms: intracellular calcium mobilization, phosphodiesterase inhibition, gamma-amino butyric acid receptor (GABA) modulation, inhibition of high ATP-dependent cyclic nucleotide transporters adenosine receptor affinity and antagonism (Aronsen *et al.,* 2014; Franco *et al.,* 2013).

Methylxanthines action in the brain: MTX-derived substances are rapidly absorbed into the gastrointestinal system and are distributed in the blood and body tissues about 45 minutes after ingestion (Arnaud, 2011). Importantly, caffeine can cross the blood-brain barrier and enter the brain by simple or facilitated diffusion; Similarly, theophylline and theobromine can also penetrate the CNS (Liu *et al.,* 2005). In the CNS, blockade of P1 receptors by MTXs seems to be the main means of action of these substances, resulting in psychostimulatory and anti-inflammatory neural effects by antagonizing adenosine receptors (Gołembiowska *et al*., 2013). From this perspective, MTXs can regulate the microglial cells action and consequently suppress the release of proinflammatory mediators and reactive oxygen species (ROS) resulting from glial cell stimulation stimulation (Gao *et al.,* 2002; Qin *et al*. 2002). The study by Matos *et al.* (2012) demonstrated that acuteexposure to the A_{2A} receptor agonist, CGS 21680, inhibited the synaptic glutamate reuptake in astrocytes, an effect avoided by the A_{2A} receptor antagonist, SCH 58261. In the last decade, other potentialities presented by MTXs have been described (Rivera and Díaz, 2014). For example, it has been reported that A_{2A} receptor antagonists prevent lipid peroxidation and increase the activity of antioxidant enzymes in brain regions of different models of neural toxicity / neurodegeneration (Nobre *et al.,* 2010; Noschang *et al.,* 2009). MTXs are substances with chemical similarities that differ in their potency in stimulating the CNS, following an order of potency: theophylline> caffeine> theobromine (Altimari *et al*., 2001; Goodman and Gilman, 2006). Regarding drugs composed of theophylline, aminophylline is an FDA approved drug to relieve symptoms of reversible airway obstruction due to asthma or other chronic lung diseases such as chronic bronchitis and emphysema (Gondal and Zulfiqar, 2019), but which also has other considerable features such as its excitatory effect on the CNS.

Aminophylline mechanism of action: Aminophylline is a drug of the MTX group and its pharmacological action is not yet fully understood. It is constituted by a combination of approximately 80% of theophylline and ethylenediamine, thus forming a theophylline ethylenediamine salt. This is because xanthines, specifically theophylline, have a very low solubility which is enhanced by the formation of saline complexes complexes (Goodman and Gilman, 2006; Bueno, 2003).



(Source: Sigma Aldrich)

Figure 3. Molecular structure of aminophylline

The basic chemical structure of theophylline consists of a xanthine ring with methylations at positions one and three, thus forming part of the group of xanthines (or methylxanthines) (Katzung, 2010). Theophylline acts in three distinct ways as described below. Theophylline causes non-selective inhibition of phosphodiesterase type III and type IV isoenzymes, which leads to tissue increase of cyclic adenine monophosphate (cAMP) and cyclic guanosine monophosphate concentrations 3 ', 5', resulting in smooth muscle relaxation in the lungs and pulmonary vessels, diuresis and CNS and cardiac stimulation (Gondal and Zulfiqar, 2019). In inflammatory conditions, the action of histone deacetylase decreases due to oxidative stress through the activation of phosphoinositide-3-kinase-delta (PI3K-delta) (Ranjani and Vinotha, 2017). Theophylline increases histone deacetylase activity and recruitment to the site of inflammation at therapeutic concentrations (To *et al.,* 2010). Such action decreases the transcription of inflammatory genes that require histone acetylation to activate their transcription and also decreases the resistance to steroids in macrophages (Cosio *et al.,* 2004). Theophylline strongly antagonizes the adenosine receptor A_1, A_{2A} and A_3 to a lesser intensity. Theophylline also increases calcium uptake through adenosine-mediated calcium channels in the diaphragm, leading to greater contraction and reversal of diaphragm fatigue (Polosa and Blackburn, 2009). In the CNS, adenosine provides na inhibitory tone to various brain regions, and behavioral stimulation of caffeine and theophylline is attributed to non-selective adenosine A_1 and A_{2A} receptor antagonism (Oñatibia *et al.,* 2016).

Theophylline in Parkinson's Disease: Evidence that theophylline provides neuroprotection in PD patients is limited, and clinical trials provide positive (Mally and Stone, 1994) and negative (Kulisevsky *et al.,* 2002) results. Therefore, further human studies are required. The neuroprotective benefits of theophylline consumption shown in animal models of PD were mainly attributed to the antioxidant properties of its polyphenolic constituents (Weinreb *et al*., 2004; Guo *et al*., 2007). However, Xu *et al.* (2010) reported that theophylline, as an adenosine A_1 and A_{2A} receptor antagonist, significantly attenuated striatal dopamine loss in PD model mice with MPTP, similar to what caffeine does (Xu *et al.,* 2010).

Adenosine and dopamine receptor interaction in the striatum: In the CNS, there are several neurotransmitters responsible for acting as endogenous modulators, altering cellular functioning, providing the regulation of physiological activities in various organs, tissues and cells (Fredholm *et al.,* 2011). Pioneering studies such as those by Fuxe and Ungerstedt (1974) have demonstrated the modulating effects that adenosine exerts on the dopaminergic system, and this continues to be the subject of investigations for its relevance in human pathologies, such as schizophrenia and PD. The study showed that there are antagonistic interactions between adenosine and dopamine, proving that adenosine can inhibit various effects of dopamine on the cerebral cortex and basal nuclei. In this context, adenosine is not only an essential intracellular component, but also has neuromodulatory function and acts through receptor subtypes present on cell membranes, both under physiological and pathological conditions. In the CNS, adenosine modulates sleep, arousal, locomotion, nociception, neuroprotection, and various other major physiological processes (Schwarzschild *et al*., 2003; El Yacoubi *et al.,* 2000).

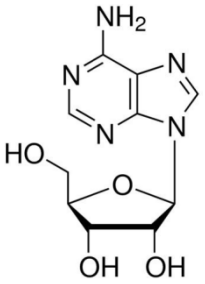
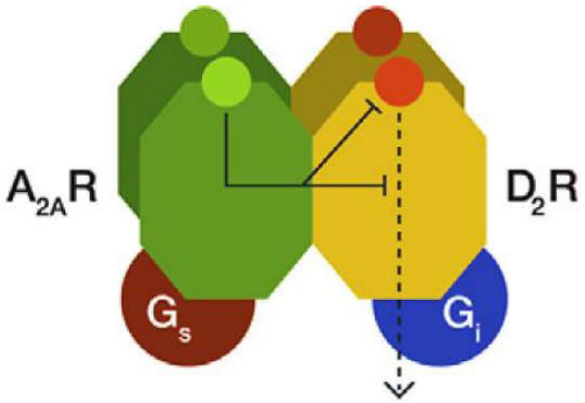


Figure 4. Adenosine molecular structure (Source: Sigma Aldrich)

Molecularly, adenosine is a nucleoside derived from adenosine triphosphate (ATP). Its action occurs through P1 purinergic receptors, which are divided into four distinct subtypes, A_1, $A_{2A,}$ A_{2B} and A_3, which are classified as metabotropic receptors, that is, they have seven transmembrane domains and are coupled to G protein.The A_1 and A_3 receptors are coupled to the Gi/o type G protein, while the A_{2A} and A_{2B} receptors are coupled to the Gs type G protein. Moreover, they may also be in the form of monomers, homodimers, heterodimers and oligomers, for example, A_1-A_1, A_{2A}-C_{B1}, A_{2A}-D_2 (Fredholm *et al.,* 2011). Methylxanthines act mainly in the adenosinergic system, including caffeine (extracted from coffee beans), theophylline (extracted from cocoa beans and tea leaves and yerba mate) and theobromine (extracted from cocoa beans), which is considered a class of psychostimulating and neuroprotective substances for reducing CNS oxidative and inflammatory stress stress (Gołembiowska *et al.,* 2013; Schiffmann *et al.,* 2007; Doré *et al.,* 2011). These natural alkaloids are the first adenosine antagonists described in the literature, demonstrating a non-selective micro molar affinity for these receptors (Müller and Jacobson, 2014). Experimental evidence suggests that the central stimulating properties of methylxanthines demonstrate beneficial therapeutic effects in the PD preventive treatment (Chen *et al.,* 2010; Goetz *et al*., 2005; Fredholm *et al.,* 1999). Such anti-parkinsonian properties occur by blocking striatal adenosine A_{2A} receptors (Ferré *et al*., 2001; Svenningsson *et al*., 1999). Thus, adenosine provides an inhibitory tone to various brain regions and stimulation of motor behaviors promoted by caffeine and theophylline is attributed to non-selective adenosine A_1 / A_{2A} receptor antagonism (Brundege and Dunwiddie, 1997). A precursor study conducted with monkeys showed that systemically treated animals with low and intermediate doses of 8-phenylteophylline, theophylline, caffeine, 8-cyclopentene-theophylline and isobutyl-1-methylxanthine showed improvement in locomotor activity that was suppressed by high doses of 5'-N-ethylcarboxamide adenosine (NECA), indicating that this drug may antagonize the behavioral suppressive effects of adenosine analogs such as NECA. Thus, suggesting that the psychomotor stimulating effects of methylxanthines are linked to their antagonistic actions on adenosine receptors (Spelman, 1988).

Neuroprotection and motor activation are characteristic effects of methylxanthine group substances, demonstrating their important therapeutic potential in neurodegenerative diseases, as well as helping in the physiological understanding of each of these pathways. Studies have also shown that the stimulation of motor activity exerted by adenosine antagonists is inhibited by blocking dopamine receptors or by depleting this neurotransmitter. As well as, motor stimulation that is induced by dopaminergic agonists are inhibited by

adenosinergic agonists and potentiated by adenosine antagonists (Ferré *et al.,* 1997; Franco *et al*., 2000). The activation of adenosine receptors A_1 and A_{2A} can modulate the dopaminergic system (Dunwiddie and Masino, 2001; Fisone; Borgkvist; Usiello, 2004). Type A_1 receptors are widely distributed throughout the brain (eg hippocampus, cerebral cortex, thalamus and cerebellum), where they regulate neurotransmitter release and neuronal firing. Acting on type A_1 receptors located in the presynaptic region, adenosine suppresses the release of various neurotransmitters (including glutamate and dopamine), while postsynaptic activation of these receptors induces neuronal hyperpolarization (Brundege and Dunwiddie, 1997). This inhibitory activity, which is increased under neurotoxic conditions, places adenosine as an important agent in neuroprotective mechanisms (Brundege and Dunwiddie, 1997; Ralevic and Burnstock, 1998). A_2 receptors are particularly expressed in regions rich in dopamine receptors, where they co-localize with D_2-type receptors (Fink *et al.,* 1992; Ferré *et al*., 2016; Ferré *et al*., 2018). Activation of adenosine A_{2A} receptors reduces D_2 receptor activity to dopaminergic agonists, including the endogenous dopamine ligand (Ferré *et al.,* 1997; Ferré *et al.,* 1991). In NB, adenosine neuromodulation plays a crucial role in motor control (Ferré*et. al.,* 1997). Several behavioral studies indicate that activation or blocking of adenosine A2 receptors inhibits or stimulates, respectively, dopamine D_2 receptor mediated effects, probably through direct interaction between adenosine A_2 and dopamine D_2 receptors (Barraco *et. al.,* 1993; Ferré *et. al.,* 1992; Morelli *et al.,* 1994; Ongini and Fredholm, 1996). In the striatum, which is the major input structure of NB, A_{2A} receptors are selectively expressed and co-located with dopamine D_2 receptors in a subpopulation of pale globe projected neurons (Fink *et al.,* 1992; Schiffmann *et al.,* 1991; Ferré *et al*., 2016; Ferré *et al*., 2018). These striatal-palatal neurons constitute the indirect pathway, one of the two major striatal exit pathways that controls the activity of NB exit nuclei, i.e. SNr and the entopeduncular nucleus.



Source:http://www.sciencedirect.com/science/article/pii/S0028390815002099?via%3Dihub.

Figure 5. Illustrative scheme demonstrating the existence of receptor complexes forming A2A-D2 heterodimers co-located in the striatum

In contrast, striato-nigral and striate-entopeduncular neurons, regulated by A_1 and D_1 receptors (Ferré *et al.,* 1997), constitute the direct NB pathway. The direct and indirect route has opposite effects on motor activity (Albin *et al.,*1989). Systemic A_{2A} receptor blockade stimulated D_1 and D_2 receptor-dependent contralateral rotations in 6-hydroxydopamine-injured rats (Fenu *et al*., 1997; Pinna *et al*., 1996; Pollack and Fink, 1996). In addition, systemic administration of A_{2A} receptor antagonists reversed receptor blockade-induced catalepsy or dopamine depletion and potentiated the anti-cataleptic effects of L-DOPA (Hauber *et al.,* 1998; Hauber *et al*., 2001; Kanda *et al*., 1994; Kanda *et al*., 1998; Shiozaki *et al*., 1999). The synergistic or antagonistic motor effects mediated by A_{2A} and D_2 receptor ligands could be explained by direct interactions between A_{2A}-D_2 receptors in striatal palatal neurons (Ferré *et al*., 1997). In contrast, interactions between the direct and indirect pathways may explain the synergistic and antagonistic motor effects of A_{2A} and D_1 receptor ligands (Ferré*et al.,* 1997; Pinna *et al.,* 1996), since the respective receptors are localized in separate populations of striatal neurons. Behavioral data suggest that interactions between A_{2A}-D_1 receptors (Fenu *et al.,* 1997; Pinna *et al.,* 1996; Pollack and Fink, 1996; Stromberg *et al*., 2000). On the other hand, it has been shown that adenosine receptor agonists produce hypomobility (Durcan and Morgan, 1989) and have anxiolytic effect in mice (Jain *et. al.,* 1995), being the motor effect attributed to A_2 receptors and the anxiolytic effect to A_1 receptors (Jain *et. al.,* 1995). However, some agonists induce changes in biphasic behavior, such as 5 ', N-Ethylcarboxamidoadenosine (NECA) a non-selective adenosine receptor agonist and 2-chloro-N6-cyclopentyladenosine (CCPA) A_1 selective, in low doses stimulate and in high doses inhibit locomotion (Florio*et al.,* 1997). Adenosine receptor agonists may further induce catalepsy (Ferré *et al.,* 1991; Zarrindast *et al.,*1993) or potentiate dopamine antagonist-induced catalepsy (Khisti; *et al*., 2000).

Several studies have used different PD experimental models, with the induction of symptoms by neurotoxins such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), 6-hydroxydopamine (6-OHDA) and drugs, that block thecentral dopaminergic receptors in the striatum such as haloperidol, which is widely used to induce PD in animal models and through which certain aspects of the disease, such as catalepsy, motor imbalance, and slowness of movement can be reproduced experimentally (Fang *et al*., 2010; González *et al*., 2010; Ho *et al.,* 2011). A study of 118 Wistar rats demonstrated that haloperidol-induced catalepsy was reversed by the systemic administration of high doses of anticholinergic theophylline, resulting in a significant reduction in catalepsy intensity in animals evaluated by the bar catalepsy test (González *et al.,* 2010). Thus, the validated working body demonstrated that this interaction between dopamine and adenosine receptors offers new therapeutic possibilities for Parkinson's disease and other neuropsychiatric disorders that present striatopalid neuron dysfunction. Therefore, providing essential data for further research that increases the neurophysiology understanding of NB.

Final Considerations

Parkinson's disease is a chronic and progressive disorder of the nervous system and its incidence and prevalence increases in older age groups. The onset of the disease usually occurs between 50 and 70 years of age, and patients with early onset of the disease may be found (Meneses *et al.,* 1996). The available pharmacological treatments are based on restoring dopaminergic activity to improve functional mobility, increasing patients' quality of life. Levodopa (L-dopa) is the treatment of choice for this disease, however the presence of adverse effects caused by this drug makes its use cautious

(Rodrigues and Campos, 2006). In order to overcome or alleviate the limitations of L-dopa use, dopaminergic agonists were inserted, highly effective in treating the early stages of the disease, but not significantly modifying the disease progression. But new pharmacological manipulations for the PD treatment should produce agents with anti-Parkinsonian action at all stages of the disease, without losing the drug efficacy and preventing complications (Jenner, 2003; Júri and Chaná, 2006). The study of new therapies for Parkinson's disease focuses on non-dopaminergic systems inside the base nuclei that go beyond the injured nigrostriatal pathways (Brotchie, 1998; Jenner, 2000). Several agents providing therapeutic potential have been described, including agents acting on adenosine, glutamatergic, cannabinoid, opioid, α2-adrenergic receptors and nicotinic and muscarinic cholinergic receptors. The experimental evidence presented here suggests that the central stimulating properties performed by methylxanthines are neuroprotective and demonstrate beneficial therapeutic effects in the treatment of PD. These results corroborate the hypothesis of a strong interaction between adenosine and dopamine receptors in the striatal middle spinous neurons, playing opposite roles. Thus, studies aimed at clarifying the effect of different adenosine receptor antagonists, especially their action on A2A-D2 heterodimer complexes, are important to better elucidate their neuromodulatory role in PD. Evaluating the importance of the subject, and the results of the previously mentioned studies, it is considered relevant to carry out new research. Knowledge of the basal nuclei physiology and PD pathophysiology, the high incidence and prevalence of PD, and the emergence of side effects related to the continued use of dopaminergic therapy need to be further elucidated.

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