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Epigenetic Modulation of Adenosine A_{2A} Receptor: A Putative Therapeutical Tool for the Treatment of Parkinson's Disease

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1. Introduction

Adenosine is a nucleoside distributed throughout the entire organism as an intermediary metabolite. At the extracellular level, adenosine plays multiple physiologic roles, interacting with specific receptors: A_1, A_{2A}, A_{2B} and A_3 (Fredholm et al., 2001). While the A_1Rs and A_3Rs are coupled in an inhibitory way to adenylate cyclase through the $G_{\alpha i/o}$ protein, the A_2Rs are coupled in a stimulatory way to this enzymatic activity through $G_{\alpha s}$ protein (Ralevic & Burnstock, 1998).

Adenosine levels are increased after ischemia, hypoxia, excitotoxicity, inflammation and cerebral lesions. In these situations, it is considered that high adenosine levels play a neuroprotective role (Ribeiro et al., 2002). Interestingly, adenosine regulates the release of glutamate, the main excitatory neurotransmitter of the nervous system (Sebastiao & Ribeiro, 1996). A_1Rs are widely expressed in the brain and have been shown to modulate neuronal excitability by decreasing pre-synaptic release of various neurotransmitters (Fredholm & Dunwiddie, 1988). The most dramatic inhibitory actions are on the glutamatergic system (Masino et al., 2002). In the central nervous system (CNS), A_1Rs are associated with neuroprotective processes (Angulo et al., 2003; Dunwiddie and Masino, 2001). Moreover, they are upregulated in human neurodegenerative diseases with abnormal protein aggregates and it is related to compensatory mechanisms (Albasanz et al., 2007, 2008; Angulo et al., 2003; Perez-Buira et al., 2007; Rodríguez et al., 2006). Regarding A_{2A}Rs, these

receptors are concentrated in the striatum, modulating dopaminergic activity, but they are also present in the hippocampus and cerebral cortex, modulating the glutamate release in the brain. Adenosine activity through A_2 receptors (A_{2A}Rs) can eventually give rise to neurotoxicity, neuronal damage and cellular death (de Mendoça et al., 2000). In fact, A_{2A}Rs activity is associated with the outcome of cerebral injury as well as the development of Aβ-induced synaptotoxicity (Canas et al., 2009; Cunha, 2005; Stone et al., 2009).

2. Human brain A_{2A}R localization and implications in PD pathophysiology

As mentioned in the previous section, A_{2A}Rs are G protein-coupled receptors that stimulate adenylyl cyclase through $G_{\alpha s}$ proteins, promoting accumulation of intracellular cAMP (Van Calker et al., 1979). The activation of these receptors mediates multiple physiological effects of adenosine, both in the CNS and in peripheral tissues (Fredholm et al., 2001). Pharmacological activation of A_{2A}Rs promotes vasodilatation, immunosuppression, tissue protection, sleep promotion and depression (Cerqueira, 2004; El Yacoubi et al., 2003; Linden, 2001; Satoh et al., 1998).

A_{2A}Rs are widely expressed, but they are highly concentrated in spleen, thymus, leukocytes and blood platelets. A_{2A}Rs levels in immune cells play a critical role in the protection of normal tissues by attenuating inflammation and tissue damage *in vivo* (Ohta and Sitkovsky, 2001). In the CNS, A_{2A}Rs are highly expressed in the striatum (Peterfreund et al., 1996; Schiffmann et al., 1991). Most striatal neurons (95%) are GABAergic medium spiny neurons (MSNs) which can be divided into two subtypes. One subpopulation projects to the globus pallidus and contains enkephalin. The other subpopulation projects to the substantia nigra and contains substance P and dynorphin. These neurons receive inputs from glutamatergic afferents from cortical, thalamic and limbic areas and dopaminergic afferents from the substantia nigra pars compacta and the ventral tegmental area. MSNs promote two striatal efferent pathways, the "direct" and "indirect", affecting motor activation and inhibition, respectively. The MSNs of the direct pathway correspond to the subpopulation containing dynorphin and they also express dopamine D_1 receptors, whereas indirect MSNs express enkephalin, dopamine D_2 receptors (D_2Rs) and A_{2A}Rs (Schiffmann et al., 2007). In these cells, A_{2A}Rs physically interact (oligomerize) with D_2R, and this receptor-receptor interaction results in a tidy adenosine/dopamine functional interaction controlled by the A_{2A}R/D_2R oligomer. Consequently, two reciprocal antagonistic A_{2A}R/D_2R interactions have been described, namely an intermembrane interaction in which A_{2A}R mediates the inhibition of D_2R, thus modulating neuronal excitability and neurotransmitter release, and an interaction at the level of adenylyl-cyclase in which D_2R inhibits A_{2A}R-mediated protein phosphorylation and gene expression (for review see Ciruela et al., 2011). As a result of this interaction, antagonists of A_{2A}Rs have recently emerged as a leading candidate class of non-dopaminergic anti-parkinsonian agents, based in part on the unique CNS distribution of A_{2A}Rs and A_{2A}R/D_2R oligomers (Fuxe et al., 2003). Moreover, the metabotropic glutamate receptors 5 ($mGluR_5$s) are co-localized in the same GABAergic striatal output neurons and in glutamatergic nerve terminals in the striatum, and they form heteromeric complexes with A_{2A}Rs (Ferré et al., 2002; Rodrigues et al., 2005). This co-localization provides a morphological framework for the existence of multiple $mGlu_5$/A_{2A}/D_2 receptor interactions (Cabello et al., 2009). Thus, it is proposed that the increase in glutamate and adenosine extracellular levels activates A_{2A}R and $mGluR_5$, both synergizing and promoting the inhibition of D_2Rs (Ferré et al., 2007).

Of note is the characterization of A_1R-$A_{2A}R$ heteromers with antagonistic activities between the two receptors, preferentially at presynaptically level in glutamatergic terminals of cortico-striatal afferents to the MSNs (Ciruela et al., 2006; Quiroz et al., 2009). Under baseline conditions, reduced levels of extracellular adenosine stimulate the activity of A_1Rs while glutamatergic neurotransmission is inhibited. Under conditions of neuronal excitability, the extracellular adenosine levels are increased, showing $A_{2A}Rs$ affinity and inhibiting A_1R activity, and promoting the release of glutamate, which in turn also increases activation of $mGluR_5$ synergizing with $A_{2A}Rs$ and thereby facilitating more glutamate release (Rodrigues et al., 2005).

Interestingly, striatal $A_{2A}Rs$ expression levels have been found to be increased in PD patients with dyskinesias; this upregulation is attributed to the effect of levodopa (L-dopa) treatment (Calon et al., 2004). Recently, it has been proven that high $A_{2A}Rs$ levels in the striatum and in lymphocytes correlate with motor symptoms in PD patients who were previously either not pharmacologically treated or were treated with a wide spectrum of drugs and not restricted to only L-dopa (Varani et al., 2010). Therefore, $A_{2A}R$ upregulation in PD, which tonically inhibits D_2R (see above), together with the low dopamine content in the striatum, a consequence of the death of dopaminergic neurons from the substantia nigra, contribute to a synergistic impairment of D_2R function.

It remains to be clarified whether upregulation of $A_{2A}Rs$ levels in PD is a hallmark of the disease or is a consequence of dopaminergic terminal drop-off in the striatum. This issue has been quite controversial, as increased striatal levels of $A_{2A}Rs$ were shown in 6-hydroxidopamine (6-OHDA)-treated rats, as a consequence of dopamine denervation (Pinna et al., 2002), and also in 6-OHDA-treated rats with intermittent L-dopa treatment (Tomiyama et al., 2004).

3. Clinical trials with $A_{2A}R$ antagonists in PD

L-dopa remains the most effective treatment for symptomatic relief of PD, although its pharmacological administration over time induces motor dysfunctions such as dyskinesias (Obeso et al., 2000). One of the strategies to reduce these is the administration of non-dopaminergic drugs that modulate dopaminergic neurotransmission. Indeed, $A_{2A}R$ has emerged as a potential pharmacological target in PD, as its relationship with the dopaminergic system has been clearly demonstrated (Ferré et al., 2002). There have been several clinical trials with $A_{2A}R$ antagonists, such as istradefylline (also known as KW-6002), confirming that their administration to PD patients reduces the "OFF" time and dyskinesias induced by L-dopa treatment (Bara-Jimenez et al., 2003; Factor et al., 2010; Hauser et al., 2003, 2008; LeWitt et al., 2008b; Mizuno et al., 2010; Stacy et al., 2008). As $A_{2A}Rs$ expression levels are nearly exclusive of the striatum, the use of specific antagonists for these receptors could promote a specific brain-area effect (Brooks et al., 2008). Interestingly, it has recently been described how KW-6002 preferentially targets the $A_{2A}R$ within the postsynaptic $A_{2A}R/D_2R$ oligomer located at the MSNs, thus potentiating D_2R-mediated motor activation (Orru et al., 2011). Therefore, although the use of istradefylline as a monotheraphy in PD has not been statistically demonstrated (Fernandez et al., 2010), its administration as a coadjuvant seems to allow a reduction in the L-dopa dose.

As mentioned before, there are heteromers formed by $A_{2A}R$, D_2R and $mGluR_5$ in striatal GABAergic neurons or MSNs (Cabello et al., 2009). It is proposed that the increase in glutamate and adenosine extracellular levels activates $A_{2A}R$ and $mGluR_5$, both synergizing

and promoting the inhibition of D_2Rs (Ferré et al., 2007). Interestingly, it has been demonstrated in a rat model of PD that the simultaneous inhibition of A_{2A}R and $mGluR_5$ synergistically reverses the parkinsonian deficits in these animals (Coccurello et al., 2004). In this line, the use of mGluR type I antagonists as a therapy for PD has been proposed (Bonsi et al., 2007). Overall, this explains why pharmaceutical companies are going after either single compounds or combinations of drugs that will simultaneously antagonize A_{2A}R and $mGluR_5$.

4. Brain DNA methylation

Studies in mice deficient in enzymes that control DNA methylation and the results of folate-free diets have established an important role for methylation in the development of the nervous system (Waterland & Jirtle, 2003). In fact, the manipulation of methylation and acetylation affects neuronal vulnerability in experimental models of neurodegenerative diseases (El-Maarri, 2003). It has also been proposed that memory processes are highly related with the level of neuronal methylation (Day & Sweatt, 2010; Liu et al., 2009).

DNA methylation is a normal process that occurs during mammal embryo development, and it is also implicated in X-chromosome inactivation and repression of proviral genes and endogenous transposons. This chemical modification is one of the most important epigenetic mechanisms in gene silencing in mammals. It is characterized by the methylation of cytosines that precede guanines in the well-known CpG sites. Those genome CpG-rich regions are called CpG islands (CGIs); they present a size between 200 bp and several kilobases. In general, these active gene promoter regions are not methylated, while the inactive gene promoter regions are fully methylated. Most CGIs are found in 5' UTR regions and in the first exon, although they can be found in regions distal to the transcription start site and in intronic regions. In normal tissues, CGIs are usually non-methylated, while they are methylated in tumorous cells, especially in tumor repressor genes (Illingworth & Bird, 2009; Jones, 1999).

Methylation of CpG sites is achieved by the action of DNA metyltransferases (Dnmt) which catalyze the transfer of a methyl group from S-adenosyl-L-methionine (SAM) to DNA. The human DNA Methylome map has recently been published, annotating those genes found methylated in normal tissues and in human diseases such as Alzheimer's disease (AD) and schizophrenia (SZ) (Ballestar & Esteller, 2008). DNA methylation in the CpG sites interferes with gene expression in two ways. The first is interference with the binding of transcription factors to DNA through the methyl group. The second is caused by the binding of specific proteins, such as $MeCP_2$, MBD1 and MBD2, to methyl CpG sites (methyl-CpG-binding proteins, MBDs). These MBDs recruit histone-modifying and chromatin-remodeling complexes to methylated sites (Portela & Esteller, 2010). The importance of these proteins is demonstrated by Rett syndrome, a disease causing severe mental dysfunction and brought on by $MeCP_2$ mutations (Amir et al., 1999).

The role of DNA methylation in the brain is an emerging field of research. Neuronal DNA methylation is modified with lifespan, and the analysis of 12 loci related with AD has revealed an age-specific epigenetic drift in the percentage of DNA methylation (Siegmund et al. 2007; Wang et al., 2008). Moreover, the degree of gene methylation varies among the different cerebral regions, and it has been reported that DNA methyltransferase 1 (Dnmt1) expression levels are different in the various cerebral regions (Ladd-Acosta et al., 2007).

Interestingly, Dnmt 1 is increased in the cortical interneurons where the GAD67 gene is suppressed in SZ patients (Veldic et al., 2004, 2005).
Finally, epigenetic therapies such as the use of demethylating agents are widely established in the treatment of tumors (Herranz & Esteller, 2006), but their use in neurodegeneration is poorly studied. In this line, S-adenosylmethionine (SAM) is a methyl group donor molecule necessary for DNA methylation which is reduced in AD (Linnebank et al., 2010; Morrison et al., 1996). There have been proposals to use it as a therapy for AD (Scarpa et al., 2003). Its administration to cell lines down-regulates PSEN1 and reduces β-amyloid production. In contrast, deprivation of SAM up-regulates PSEN1, increasing β-amyloid deposits in APP transgenic mice (Fuso et al., 2005, 2008). Interestingly, mice treated with L-methionine downregulate GAD67 and reelin levels by increasing DNA methylation of their respective gene promoter regions (Tremolizzo et al., 2002).

5. Endogenous SAM biosynthesis cycle and alterations in PD

SAM is the main biological methyl donor molecule in the methionine metabolic cycle, which is involved in the methylation of DNA, and protein, lipid and polyamine synthesis. Moreover, it is a precursor of glutathione in the liver and also perhaps in the brain (Vitvitsky et al, 2006). When SAM is demethylated, it is transformed into S-adenosylhomocysteine (SAH) which in turn is hydrolysed into homocysteine (HCY) and adenosine. To prevent the accumulation of HCY, it is remethylated to form methionine (Chiang et al., 1996; Lu, 2000) (see Figure 1). The SAM/SAH ratio is also known as methylation potential and its endogenous maintenance is very important.
L-dopa is the conventional drug used in the treatment of PD to minimize the lack of endogenous dopamine in these patients (Lewitt, 2008a; Tolosa et al., 1998). However, chronic treatment with L-dopa has been associated with hyperhomocysteinemia in plasma, peripheral tissues and brain of PD patients, as L-dopa metabolism requires S-adenosylmethionine (SAM) as a methyl donor (Lu, 2000; Müller et al., 2009a; Nutt, 2008; O'Suilleabhain et al, 2004; Zoccolella et al., 2006, 2009, 2010). Interestingly, it has been shown that L-dopa treatment in mice depletes the brain SAM content (Liu et al., 2000). In addition, elevated plasma homocysteine (Hcy) levels have been related to cognitive and motor impairment and have also been associated with the pathogenesis of other neurological diseases such as stroke and AD (Morris, 2003; Quadri et al., 2004; Seshadri et al., 2002). Interestingly, some polymorphisms described in *MTHFR* gene (methylenetetrahydrofolate reductase) have been associated with a reduction in its enzymatic activity, promoting an increase in the Hcy levels in L-dopa-treated PD patients (Frosst et al., 1995; Yasui et al., 2000). Vitamin B_6 enhances the direct flow of Hcy to cysteine, the precursor of gutathione. Deficits in vitamin B_6 induce oxidative stress and, in turn, enhance Hcy (Obeid et al., 2009). Therefore, several factors have been related with hyperhomocysteinemia and a concomitant reduction in the SAM levels in blood and cerebrospinal fluid of L-dopa-treated PD patients (Cheng et al., 1997). These include the following: 1. An excessive production of S-adenosylhomocysteine (SAH) when L-dopa is metabolized by catechol-O-methyltransferase (COMT), depleting the SAM levels an in turn decreasing the SAM/SAH ratio; 2. Reduced MTHFR enzymatic activity; and 3. Vitamin B_{12} or folic acid deficits (Dos Santos et al., 2009; Miller et al., 2003; Müller et al., 2001, 2009b; Woitalla et al., 2004). In this context, some clinical trials have been carried out using decarboxylase and COMT inhibitors (for instance, carbidopa and entacapone/tolcapone, respectively) or vitamin B_{12} and folate

supplementation to reduce Hcy levels in PD patients (Müller et al., 2003, 2006; Zoccolella et al., 2007).

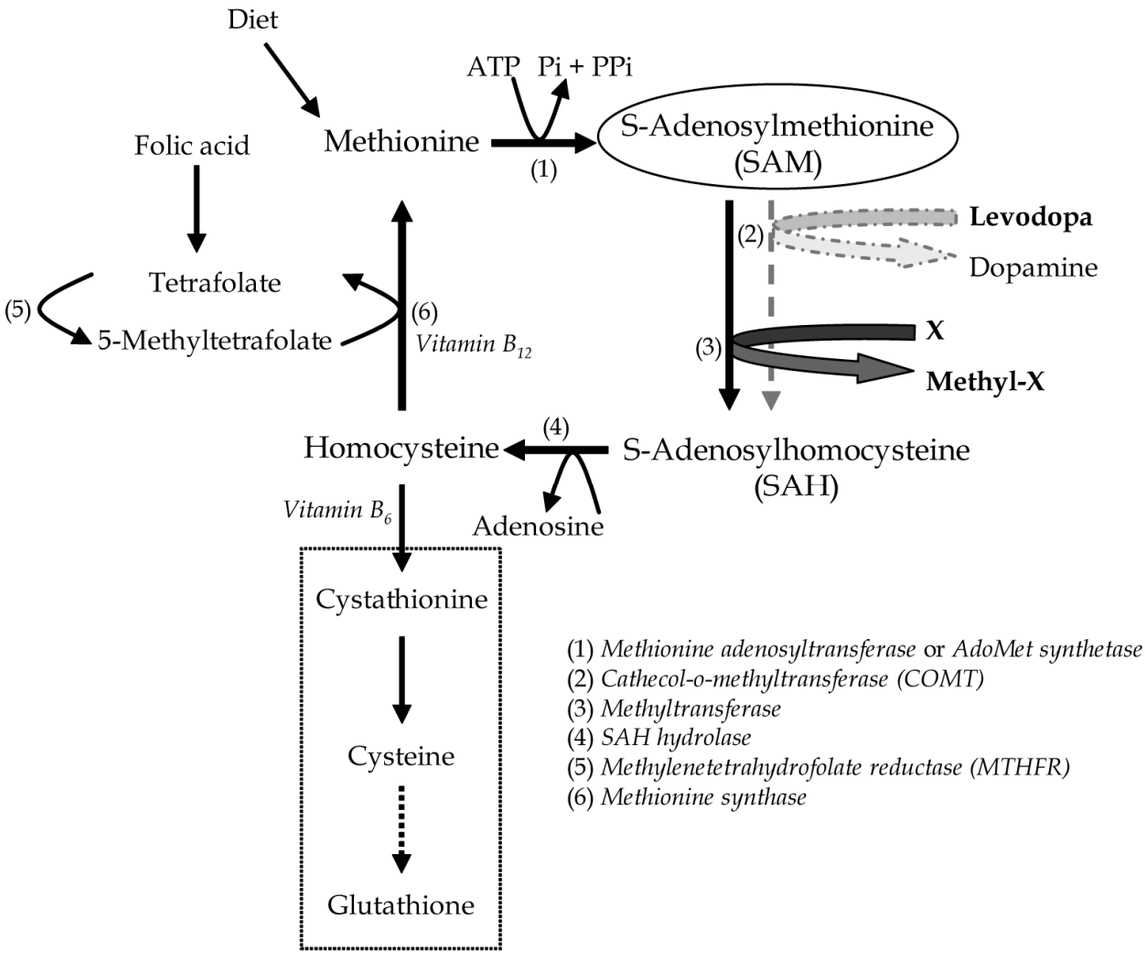

Fig. 1. SAM biosynthesis cycle

6. Epigenetic study of *ADORA2A*

$A_{2A}R$ gene (ADORA2A) is localized to chromosome 22 (Le et al., 1996; MacCollin et al., 1994; Peterfreund et al., 1996). It consists of two coding exons (exon 2 and 3) separated by a single intron of nearly 7 Kb. The exon 1 is a non-coding exon which is located at 5′ upstream exon 2 and presents 6 tissue-specific isoforms: h1A-h1F (Yu et al., 2004) (Figure 2A). Interestingly, differential expression of these isoforms has been reported in granulocytes of patients suffering from sepsis, indicating that 5′ UTR plays an important regulatory role in $A_{2A}R$ expression (Kreth et al., 2008). We recently identified a functional CGI surrounding the h1E isoform, demonstrating that DNA methylation controls basal *ADORA2A* expression in several cell lines and that it is one of the molecular mechanisms responsible for $A_{2A}Rs'$ differential expression levels in specific human brain areas, such as the putamen and the cerebellum (Buira et al., 2010a, 2010b). Interestingly, we showed that $A_{2A}R$ expression levels can be modulated by SAM treatment in SH-SY5Y (human neuroblastoma) and U87MG

(human glioblastoma) cell lines. In this context, A_{2A}Rs levels have been reported to be upregulated in PD patients (Calon et al., 2004; Varani et al., 2010). Therefore, we postulated that SAM treatment could represent a therapeutical tool to reduce A_{2A}Rs levels in these patients. This is based on the fact that the DNA methylation profile of striatal *ADORA2A* in PD patients is lower than the one found in SH-SY5Y and U87MG cells (Figure 2B). Therefore, as A_{2A}Rs cell surface levels are reduced in these cells after SAM treatment, due to an increase in the DNA methylation profile of *ADORA2A* (Buira et al., 2010a), it is also plausible that the same mechanism of action could play a role in the striatum of PD patients.

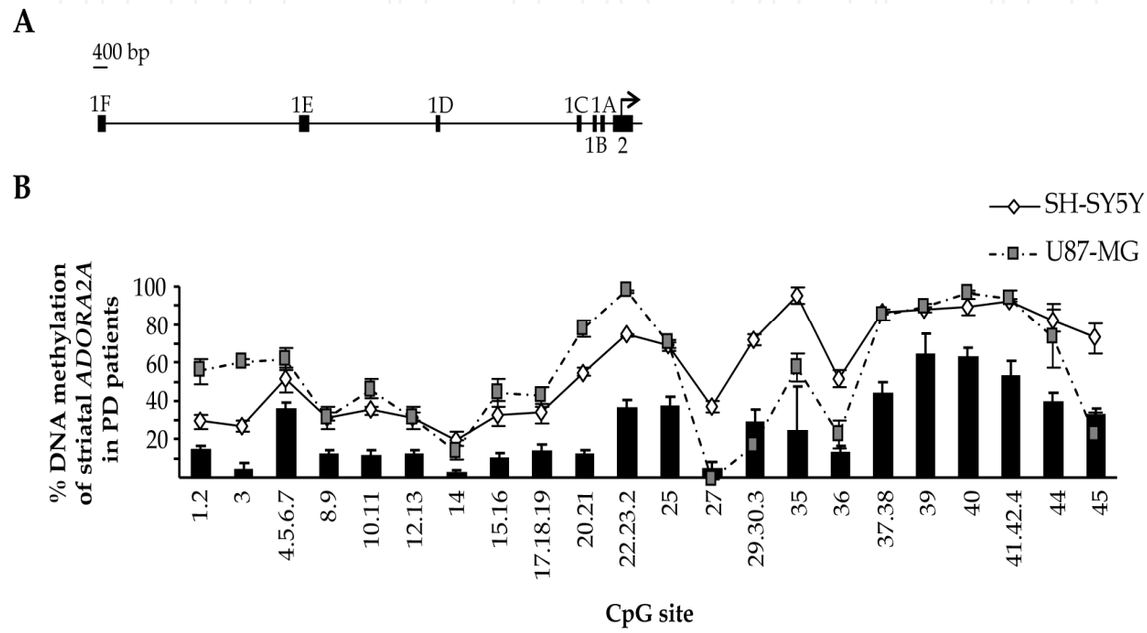

Fig. 2. A, Scaled representation of 5′ UTR region of human *ADORA2A* gene, containing 6 isoforms of non-coding exon 1 (1A-1F). Two CGIs surrounding exon 1E were recently described (Buira et al., 2010b). The translational start site (ATG) is indicated with an arrow. B, DNA methylation percentage (mean ± SD) of a locus located in the CGIs of exon 1E of 8 human post-mortem putamens of PD (black bars) and in two cell lines (black line, SH-SY5Y, n=3; dotted lines, U87-MG, n=3).

7. Clinical trials with SAM

SAM has been widely used for the treatment of liver diseases, as it increases the glutathione content (Friedel et al. 1989). Interestingly, SAM has antidepressant properties and its long term tolerability is excellent, presenting few side effects (Bell et al., 1988; Bottiglieri & Hyland, 1994; Delle Chiaie et al., 2002; Kagan et al., 1990; Lipinski et al., 1984; Papakostas, 2009, 2010). Moreover, SAM administration in patients with depression and dementia, intravenously or orally, has shown that it crosses the blood-brain barrier, and as a result, it is detected at increased levels in the cerebrospinal fluid (Bottiglieri et al., 1990).

Impaired transmethylation potential in L-dopa-treated PD patients has been proposed (De Bonis et al., 2010). The authors argue that a possible global DNA hypomethylation in hyperhomocysteinemic PD patients could be responsible for a generalized gene expression

dysregulation and for playing a role in the outcome of the pathology. In accordance with this, another study has shown improved cognitive function in PD patients with a higher SAM/SAH ratio and higher plasma vitamin B_6 (Obeid et al., 2009). It is noteworthy that SAM treatment improved depression of PD patients in an open-label clinical trial (Di Rocco et al., 2000). In fact, vitamin dietary supplementation, including SAM, has been shown to be effective in patients with early and moderate stages of AD (Chan et al., 2008; Panza et al., 2009; Remington et al., 2009; Shea and Chan, 2008). Moreover, SAM supplementation also presented antioxidant properties in an AD animal model (Cavallaro et al., 2010). In line with this, oxidative stress is also present in early-stages of PD (Ferrer et al., 2010), which points up the benefits of SAM administration in this pathology as an adjunctive treatment.

8. Conclusions and proposals for future PD interventions

As mentioned in the introduction, it is noteworthy that inactivation of A_{2A}Rs enhances the affinity of D_2Rs for dopamine, this being the probable mechanism underlying the prodopaminergic effect of A_{2A}Rs antagonists in several clinical trials with PD patients. In this chapter, we have examined the literature which, in combination with our studies based on *ADORA2A* transcriptional regulation, has led us to propose SAM treatment as an epigenetic tool to modulate the increased expression of A_{2A}Rs in PD.

It is obvious that SAM treatment presents a broad spectrum of gene targets, and not only tumor supressor genes. However, it has been reported that SAM treatment promotes a decrease in the growth of hepatocellular carcinoma cells and liver cancer in animal models, hypothesising the methylation and repression of oncogenic gene promoters by this drug (Cai et al., 1998; Pascale et al., 1992). However, the existence of several clinical trials with SAM and the reduced number of side-effects in its administration must be taken into account. Based on our studies, and bearing in mind the restrictive expression of A_{2A}Rs in the brain (mainly in 95% of striatal neurons), we postulate that SAM treatment would have a "specific" effect on A_{2A}Rs in the brain. This would be especially true in a cerebral region where it colocalizes with D_2Rs, which in turn present reduced activity due to the low dopamine content in PD. Then, although SAM treatment would reduce the expression of hypomethylated genes, its effect on A_{2A}Rs might represent significant activation of D_2Rs.

Thus, the possible beneficial role of SAM in these patients should be examined in randomized controlled studies, examining supplementation to L-dopa (allowing a reduction of its dose) and to A_{2A}Rs antagonists (such as istradefylline), or in triple administration with both current therapies.

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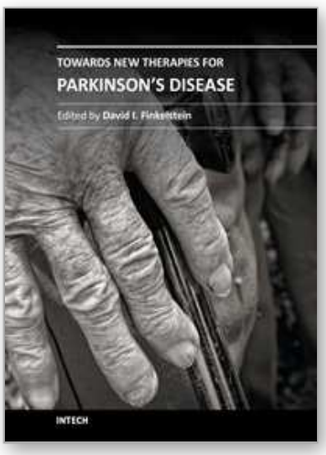

Towards New Therapies for Parkinson's Disease

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Parkinson's disease (PD) is characterised clinically by various non-motor and progressive motor symptoms, pathologically by loss of dopamine producing cells and intraneuronal cytoplasmic inclusions composed primarily of ?-synuclein. By the time a patient first presents with symptoms of Parkinson's disease at the clinic, a significant proportion of the cells in the substantia nigra have already been destroyed. This degeneration progresses despite the current therapies until the cell loss is so great that the quality of normal life is compromised. The dopamine precursor levodopa is the most valuable drug currently available for the treatment of PD. However for most PD patients, the optimal clinical benefit from levodopa decreases around five to six years of treatment. The aim of the chapters of this book is to work towards an understanding in the mechanisms of degeneration and to develop disease modifying therapies.

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