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# Epigenetic Modulation of Adenosine A<sub>2A</sub> 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<sub>1</sub>, A<sub>2A</sub>, A<sub>2B</sub> and A<sub>3</sub> (Fredholm et al., 2001). While the A<sub>1</sub>Rs and A<sub>3</sub>Rs are coupled in an inhibitory way to adenylyl cyclase through the G<sub>αi/o</sub> protein, the A<sub>2</sub>Rs are coupled in a stimulatory way to this enzymatic activity through G<sub>αs</sub> 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<sub>1</sub>Rs 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<sub>1</sub>Rs 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<sub>2A</sub>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 Mendonça et al., 2000). In fact,  $A_{2A}Rs$  activity is associated with the outcome of cerebral injury as well as the development of  $A\beta$ -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<sub>5</sub>) 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 mGluR<sub>5</sub>/ $A_{2A}$ / $D_2$  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<sub>5</sub>, both synergizing and promoting the inhibition of  $D_2Rs$  (Ferré et al., 2007).

Of note is the characterization of A<sub>1</sub>R-A<sub>2A</sub>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<sub>1</sub>Rs while glutamatergic neurotransmission is inhibited. Under conditions of neuronal excitability, the extracellular adenosine levels are increased, showing A<sub>2A</sub>Rs affinity and inhibiting A<sub>1</sub>R activity, and promoting the release of glutamate, which in turn also increases activation of mGluR<sub>5</sub> synergizing with A<sub>2A</sub>Rs and thereby facilitating more glutamate release (Rodrigues et al., 2005).

Interestingly, striatal A<sub>2A</sub>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<sub>2A</sub>R 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<sub>2A</sub>R upregulation in PD, which tonically inhibits D<sub>2</sub>R (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<sub>2</sub>R function.

It remains to be clarified whether upregulation of A<sub>2A</sub>R 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<sub>2A</sub>R 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<sub>2A</sub>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<sub>2A</sub>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<sub>2A</sub>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<sub>2A</sub>R 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<sub>2A</sub>R within the postsynaptic A<sub>2A</sub>R/D<sub>2</sub>R oligomer located at the MSNs, thus potentiating D<sub>2</sub>R-mediated motor activation (Orru et al., 2011). Therefore, although the use of istradefylline as a monotherapy 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<sub>2A</sub>R, D<sub>2</sub>R and mGluR<sub>5</sub> in striatal GABAergic neurons or MSNs (Cabello et al., 2009). It is proposed that the increase in glutamate and adenosine extracellular levels activates A<sub>2A</sub>R and mGluR<sub>5</sub>, both synergizing

and promoting the inhibition of D<sub>2</sub>Rs (Ferré et al., 2007). Interestingly, it has been demonstrated in a rat model of PD that the simultaneous inhibition of A<sub>2A</sub>R and mGluR<sub>5</sub> 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<sub>2A</sub>R and mGluR<sub>5</sub>.

#### 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 methyltransferases (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<sub>2</sub>, 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<sub>2</sub> 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  $\beta$ -amyloid production. In contrast, deprivation of SAM up-regulates PSEN1, increasing  $\beta$ -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<sub>6</sub> enhances the direct flow of Hcy to cysteine, the precursor of glutathione. Deficits in vitamin B<sub>6</sub> 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 and in turn decreasing the SAM/SAH ratio; 2. Reduced MTHFR enzymatic activity; and 3. Vitamin B<sub>12</sub> 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<sub>12</sub> and folate

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

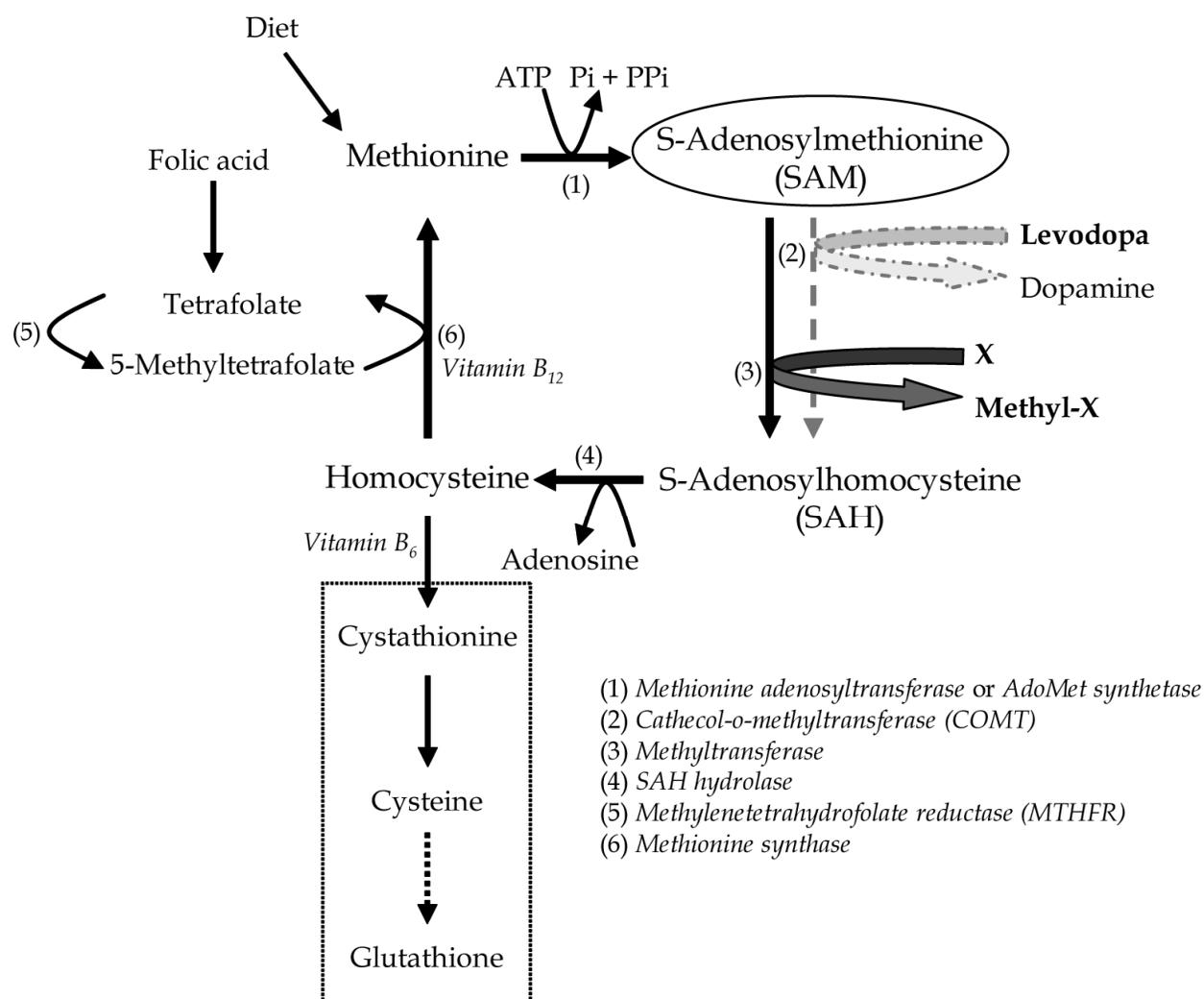


Fig. 1. SAM biosynthesis cycle

## 6. Epigenetic study of ADORA2A

A<sub>2A</sub>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<sub>2A</sub>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<sub>2A</sub>Rs' differential expression levels in specific human brain areas, such as the putamen and the cerebellum (Buirra et al., 2010a, 2010b). Interestingly, we showed that A<sub>2A</sub>R expression levels can be modulated by SAM treatment in SH-SY5Y (human neuroblastoma) and U87MG

(human glioblastoma) cell lines. In this context, A<sub>2A</sub>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<sub>2A</sub>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<sub>2A</sub>Rs cell surface levels are reduced in these cells after SAM treatment, due to an increase in the DNA methylation profile of *ADORA2A* (Buirra et al., 2010a), it is also plausible that the same mechanism of action could play a role in the striatum of PD patients.

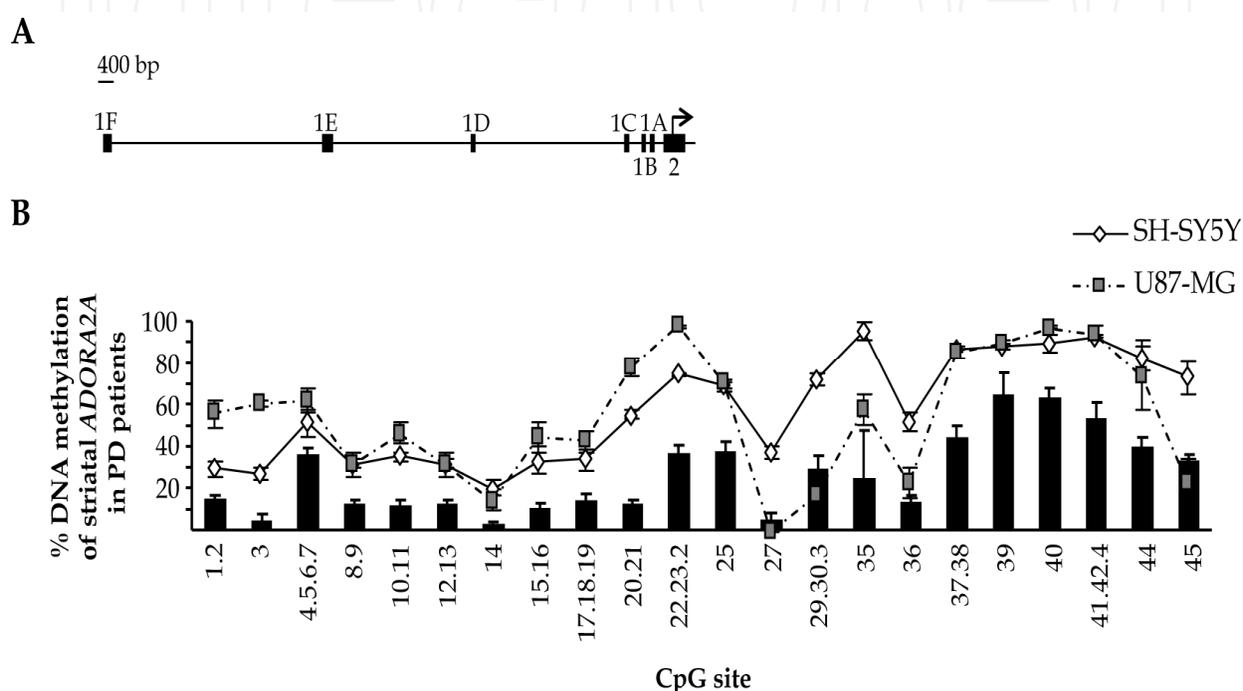


Fig. 2. A, Scaled representation of 5' UTR region of human *ADORA2A* gene, containing 6 isoforms of non-coding exon 1 (1A-1F). Two CGIs surrounding exon 1E were recently described (Buirra et al., 2010b). The translational start site (ATG) is indicated with an arrow. B, DNA methylation percentage (mean  $\pm$  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<sub>6</sub> (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<sub>2A</sub>Rs enhances the affinity of D<sub>2</sub>Rs for dopamine, this being the probable mechanism underlying the prodopaminergic effect of A<sub>2A</sub>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<sub>2A</sub>Rs in PD.

It is obvious that SAM treatment presents a broad spectrum of gene targets, and not only tumor suppressor 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<sub>2A</sub>Rs in the brain (mainly in 95% of striatal neurons), we postulate that SAM treatment would have a “specific” effect on A<sub>2A</sub>Rs in the brain. This would be especially true in a cerebral region where it colocalizes with D<sub>2</sub>Rs, 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<sub>2A</sub>Rs might represent significant activation of D<sub>2</sub>Rs.

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<sub>2A</sub>Rs antagonists (such as istradefylline), or in triple administration with both current therapies.

## 9. Acknowledgments

We are very grateful to Dr. Sandra Pérez Buira, Dr. José Luis Albasanz, Guido Dentesano and Jesús Moreno for their contributions to the study of *ADORA2A* transcriptional regulation. We thank T. Yohannan for editorial help. The experimental work described in the present chapter was funded by grants from the Ministerio de Ciencia e Innovación, (PI05/1631, CP08/00095, BFU2008-00138), the European Union through the Marie-Curie Research Training Network PRAIRIES (Contract MRTN-CT-2006-035810), the Consejería de Educación y Ciencia (PCI08-0125), the Consejería de Sanidad-FISCAM (PI-2007/50 and G-2007-C/13) of the Junta de Comunidades de Castilla-La Mancha and the Fundació La Marató de TV3 (092330, 090331).

## 10. References

- Albasanz, J.L.; Rodríguez, A.; Ferrer, I. & Martín, M. (2007). Up-regulation of adenosine A1 receptors in frontal cortex from Pick's disease cases. *The European journal of neuroscience*, Vol.26, No.12, pp. 3501-3508
- Albasanz, J.L.; Perez, S.; Barrachina, M.; Ferrer, I. & Martín, M. (2008). Up-regulation of adenosine receptors in the frontal cortex in Alzheimer's disease. *Brain pathology*, Vol.18, No.2, pp. 211-219
- Amir, R.E.; Van den Veyver, I.B.; Wan, M.; Tran, C.Q.; Francke, U. & Zoghbi, H.Y. (1999). Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. *Nature Genetics*, Vol.23, No.2, pp. 185-188
- Angulo, E.; Casadó, V.; Mallol, J., Canela, E.I., Viñals, F., Ferrer, I., Lluís, C. & Franco, R. (2003). A1 adenosine receptors accumulate in neurodegenerative structures in Alzheimer disease and mediate both amyloid precursor protein processing and tau phosphorylation and translocation. *Brain pathology*, Vol.13, No.4, pp. 440-451
- Ballestar, E. & Esteller, M. (2008). SnapShot: the human DNA methylome in health and disease. *Cell*, Vol.135, No.6, pp. 1144-1144
- Bara-Jimenez, W.; Sherzai, A.; Dimitrova, T.; Favitt, A.; Bibbiani, F.; Gillespie, M.; Morris, M.J.; Mouradian, M.M. & Chase, T.N. (2003). Adenosine A(2A) receptor antagonist treatment of Parkinson's disease. *Neurology*, Vol.61, No.3, pp. 293-296
- Bell, K.M.; Plon, L.; Bunney, W.E. Jr. & Potkin, S.G. (1988). S-adenosylmethionine treatment of depression: a controlled clinical trial. *The American journal of psychiatry*, Vol.145, No.9, pp. 1110-1114
- Bonsi, P.; Cuomo, D.; Picconi, B.; Sciamanna, G.; Tschertter, A.; Tolu, M.; Bernardi, G.; Calabresi, P. & Pisani, A. (2007). Striatal metabotropic glutamate receptors as a target for pharmacotherapy in Parkinson's disease. *Amino acids*, Vol.32, No.2, pp. 189-195
- Bottiglieri, T.; Godfrey, P.; Flynn, T.; Carney, M.W.; Toone, B.K. & Reynolds, E.H. (1990). Cerebrospinal fluid S-adenosylmethionine in depression and dementia: effects of treatment with parenteral and oral S-adenosylmethionine. *Journal of neurology, neurosurgery, and psychiatry*, Vol.53, No.12, pp. 1096-1098
- Bottiglieri, T. & Hyland, K. (1994). S-adenosylmethionine levels in psychiatric and neurological disorders: a review. *Acta neurologica Scandinavica. Supplementum*, Vol. 154, pp. 19-26
- Brooks, D.J.; Doder, M.; Osman, S.; Luthra, S.K.; Hirani, E.; Hume, S.; Kase, H.; Kilborn, J.; Martindill, S. & Mori, A. (2008). Positron emission tomography analysis of [11C]KW-6002 binding to human and rat adenosine A2A receptors in the brain. *Synapse*, Vol.62, No.9, pp. 671-681
- Buira, S.P.; Albasanz, J.L.; Dentesano, G.; Moreno, J.; Martín, M.; Ferrer, I. & Barrachina, M. (2010a). DNA methylation regulates adenosine A(2A) receptor cell surface expression levels. *Journal of neurochemistry*, Vol.112, No.5, pp. 1273-1285
- Buira, S.P.; Dentesano, G.; Albasanz, J.L.; Moreno, J.; Martín, M.; Ferrer, I. & Barrachina, M. (2010b). DNA methylation and Yin Yang-1 repress adenosine A2A receptor levels in human brain. *Journal of neurochemistry*, Vol.115, No.1, pp. 283-295

- Cabello, N.; Gandía, J.; Bertarelli, D.C.; Watanabe, M.; Lluís, C.; Franco, R.; Ferré, S.; Luján, R. & Ciruela, F. (2009). Metabotropic glutamate type 5, dopamine D2 and adenosine A2a receptors form higher-order oligomers in living cells. *Journal of neurochemistry*, Vol. 109, No.5, pp. 1497-1507
- Cai, J.; Mao, Z.; Hwang, J.J. & Lu, S.C. (1998). Differential expression of methionine adenosyltransferase genes influences the rate of growth of human hepatocellular carcinoma cells. *Cancer research*, Vol.58, No.7, pp. 1444-1450
- Calon, F.; Dridi, M.; Hornykiewicz, O.; Bédard, P.J.; Rajput, A.H. & Di Paolo, T. (2004). Increased adenosine A2A receptors in the brain of Parkinson's disease patients with dyskinesias. *Brain*, Vol.127, No.Pt 5, pp. 1075-1084
- Canas, P.M.; Porciúncula, L.O.; Cunha, G.M.; Silva, C.G.; Machado, N.J.; Oliveira, J.M.; Oliveira, C.R. & Cunha, R.A. (2009). Adenosine A2A receptor blockade prevents synaptotoxicity and memory dysfunction caused by beta-amyloid peptides via p38 mitogen-activated protein kinase pathway. *The Journal of neuroscience*, Vol.29, No.47, pp. 14741-14751
- Cavallaro, R.A.; Fuso, A.; Nicolai, V. & Scarpa, S. (2010). S-adenosylmethionine prevents oxidative stress and modulates glutathione metabolism in TgCRND8 mice fed a B-vitamin deficient diet. *Journal of Alzheimer's disease*, Vol.20, No.4, pp. 997-1002
- Cerqueira, M.D. (2004). The future of pharmacologic stress: selective A2A adenosine receptor agonists. *The American journal of cardiology*, Vol.94, No.2A, pp. 33D-40D
- Chan, A.; Paskavitz, J.; Remington, R.; Rasmussen, S. & Shea, T.B. (2008). Efficacy of a vitamin/nutriceutical formulation for early-stage Alzheimer's disease: a 1-year, open-label pilot study with a 16-month caregiver extension. *American journal of Alzheimer's disease and other dementias*, Vol.23, No.6, pp. 571-585
- Cheng, H.; Gomes-Trolin, C.; Aquilonius, S.M.; Steinberg, A.; Löfberg, C.; Ekblom, J. & Orelund, L. (1997). Levels of L-methionine S-adenosyltransferase activity in erythrocytes and concentrations of S-adenosylmethionine and S-adenosylhomocysteine in whole blood of patients with Parkinson's disease. *Experimental neurology*, Vol.145, No.2Pt1, pp. 580-585
- Chiang, P.K.; Gordon, R.K.; Tal, J.; Zeng, G.C.; Doctor, B.P.; Pardhasaradhi, K. & McCann P.P. (1996). S-Adenosylmethionine and methylation. *The FASEB journal*, Vol.10, No.4, pp. 471-480
- Ciruela, F.; Casadó, V.; Rodrigues, R.J.; Luján, R.; Burgueño, J.; Canals, M.; Borycz, J.; Rebola, N.; Goldberg, S.R.; Mallol, J.; Cortés, A.; Canela, E.I.; López-Giménez, J.F.; Milligan, G.; Lluís, C.; Cunha, R.A.; Ferré, S. & Franco, R. (2006). Presynaptic control of striatal glutamatergic neurotransmission by adenosine A1-A2A receptor heteromers. *The Journal of neuroscience*, Vol.26, No.7 pp. 2080-2087
- Ciruela, F.; Gómez-Soler, M.; Guidolin, D.; Borroto-Escuela, D.O.; Agnati, L.F.; Fuxe, K. & Fernández-Dueñas, V. (2011). Adenosine receptor containing oligomers: Their role in the control of dopamine and glutamate neurotransmission in the brain. *Biochimica et biophysica acta*, Vol.1808, No.5, pp. 1245-1255
- Coccurello, R.; Breyse, N. & Amalric, M. (2004). Simultaneous blockade of adenosine A2A and metabotropic glutamate mGlu5 receptors increase their efficacy in reversing Parkinsonian deficits in rats. *Neuropsychopharmacology*, Vol.29, No.8, pp. 1451-1461

- Cunha, R.A. (2005). Neuroprotection by adenosine in the brain: From A(1) receptor activation to A (2A) receptor blockade. *Purinergic signalling*, Vol.1, No.2, pp. 111-134
- Day, J.J. & Sweatt, J.D. (2010). DNA methylation and memory formation. *Nature neuroscience*, Vol.13, No.11, pp. 1319-1323
- De Bonis, M.L., Tessitore, A., Pellicchia, M.T., Longo, K., Salvatore, A., Russo, A., Ingrosso, D., Zappia, V., Barone, P., Galletti, P. & Tedeschi, G. (2010). Impaired transmethylation potential in Parkinson's disease patients treated with L-Dopa. *Neuroscience letters*, Vol.468, No.3, pp. 287-291
- Delle Chiaie, R.; Pancheri, P. & Scapicchio, P. (2002). Efficacy and tolerability of oral and intramuscular S-adenosyl-L-methionine 1,4-butanedisulfonate (SAME) in the treatment of major depression: comparison with imipramine in 2 multicenter studies. *The American journal of clinical nutrition*, Vol.76, No.5, pp. 1172S-1176S
- Di Rocco, A.; Rogers, J.D.; Brown, R.; Werner, P. & Bottiglieri, T. (2000). S-Adenosyl-Methionine improves depression in patients with Parkinson's disease in an open-label clinical trial. *Movement disorders*, Vol.15, No.6, pp. 1225-1229
- de Mendonça, A.; Sebastião, A.M. & Ribeiro, J.A. (2000). Adenosine: does it have a neuroprotective role after all? *Brain research. Brain research reviews*, Vol.33, No.2-3, pp. 258-274
- Dos Santos, E.F.; Busanello, E.N.; Miglioranza, A.; Zanatta, A.; Barchak, A.G.; Vargas, C.R.; Saute, J.; Rosa, C.; Carrion, M.J.; Camargo, D.; Dalbem, A.; da Costa, J.C.; de Sousa Miguel, S.R.; de Mello Rieder, C.R. & Wajner, M. (2009). Evidence that folic acid deficiency is a major determinant of hyperhomocysteinemia in Parkinson's disease. *Metabolic brain disease*, Vol.4, No.2, pp. 257-269
- Dunwiddie, T.V. & Masino, S.A. (2001). The role and regulation of adenosine in the central nervous system. *Annual review of neuroscience*, Vol. 24, pp. 31-55
- El-Maarri, O. (2003). DNA methylation and human diseases. *Advances in experimental medicine and biology*, Vol.544, pp. 135-144
- El Yacoubi, M.; Costentin, J. & Vaugeois, J.M. (2003). Adenosine A<sub>2A</sub> receptors and depression. *Neurology*, Vol.61, No.11 Suppl 6, pp. S82-S87
- Factor, S.; Mark, M.H.; Watts, R.; Struck, L.; Mori, A.; Ballerini, R.; Sussman, N.M. & Istradefylline 6002-US-007 Study Group. (2010). A long-term study of istradefylline in subjects with fluctuating Parkinson's disease. *Parkinsonism & related disorders*, Vol.16, No.6, pp. 423-426
- Fernandez, H.H.; Greeley, D.R.; Zweig, R.M.; Wojcieszek, J.; Mori, A.; Sussman, N.M. & 6002-US-051 Study Group. (2010). Istradefylline as monotherapy for Parkinson disease: results of the 6002-US-051 trial. *Parkinsonism & related disorders*, Vol.16, No.1, pp. 16-20
- Ferré, S.; Karcz-Kubicha, M.; Hope, B.T.; Popoli, P.; Burgueño, J.; Gutiérrez, M.A.; Casadó, V.; Fuxe, K.; Goldberg, S.R.; Lluís, C.; Franco, R. & Ciruela, F. (2002). Synergistic interaction between adenosine A<sub>2A</sub> and glutamate mGlu<sub>5</sub> receptors: implications for striatal neuronal function. *Proceeding of the National Academy of Sciences of the United States of America*, Vol.99, No.18, pp.11940-11945

- Ferré, S.; Ciruela, F.; Woods, A.S.; Lluís, C. & Franco, R. (2007). Functional relevance of neurotransmitter receptor heteromers in the central nervous system. *Trends in Neuroscience*, Vol.30, No.9, pp. 440-446
- Ferrer, I.; Martinez, A.; Blanco, R.; Dalfo, E. & Carmona, M. (2010) Neuropathology of sporadic Parkinson disease before the appearance of parkinsonism: preclinical Parkinson disease. *Journal of neural transmission*, 2010 Sep 23. [Epub ahead of print]
- Fredholm, B.B. & Dunwiddie, T.V. (1988). How does adenosine inhibit transmitter release? *Trends in pharmacological sciences*, Vol.9, No.4, pp. 130-134
- Fredholm, B.B.; IJzerman, A.P.; Jacobson, K.A.; Klotz, K.N. & Linden, J. (2001). International Union of Pharmacology. XXV. Nomenclature and classification of adenosine receptors. *Pharmacological reviews*, Vol.53, No.4, pp. 527-552
- Friedel, H.A.; Goa, K.L. & Benfield, P. (1989). S-adenosyl-L-methionine. A review of its pharmacological properties and therapeutic potential in liver dysfunction and affective disorders in relation to its physiological role in cell metabolism. *Drugs*, Vol.38, No.3, pp. 389-416
- Frost, P.; Blom, H.J.; Milos, R.; Goyette, P.; Sheppard, C.A.; Matthews, R.G.; Boers, G.J.; den Heijer, M.; Kluijtmans, L.A.; van den Heuvel, L.P.; et al. (1995). A candidate genetic risk factor for vascular disease: a common mutation in methylenetetrahydrofolate reductase. *Nature genetics*, Vol.10, No.1, pp. 111-113
- Fuso, A.; Seminara, L.; Cavallaro, R.A.; D'Anselmi, F. & Scarpa, S. (2005). S-adenosylmethionine/homocysteine cycle alterations modify DNA methylation status with consequent deregulation of PS1 and BACE and beta-amyloid production. *Molecular and cellular neurosciences*, Vol.28, No.1, pp. 195-204
- Fuso, A.; Nicolìa, V.; Cavallaro, R.A.; Ricceri, L.; D'Anselmi, F.; Coluccia, P.; Calamandrei, G. & Scarpa, S. (2008). B-vitamin deprivation induces hyperhomocysteinemia and brain S-adenosylhomocysteine, depletes brain S-adenosylmethionine, and enhances PS1 and BACE expression and amyloid-beta deposition in mice. *Molecular and cellular neurosciences*, Vol.37, No.4, pp. 731-746
- Fuxe, K.; Agnati, L.F.; Jacobsen, K.; Hillion, J.; Canals, M.; Torvinen, M.; Tinner-Staines, B.; Staines, W.; Rosin, D.; Terasmaa, A.; Popoli, P.; Leo, G.; Vergoni, V.; Lluís, C.; Ciruela, F.; Franco, R. & Ferré, S. (2003). Receptor heteromerization in adenosine A2A receptor signaling: relevance for striatal function and Parkinson's disease. *Neurology*, Vol.61, No.11, pp. S19-S23
- Hauser, R.A.; Hubble, J.P.; Truong, D.D. & Istradefylline US-001 Study Group. (2003). Randomized trial of the adenosine A(2A) receptor antagonist istradefylline in advanced PD. *Neurology*, Vol.61, No.3, pp. 297-303
- Hauser, R.A.; Shulman, L.M.; Trugman, J.M.; Roberts, J.W.; Mori, A.; Ballerini, R.; Sussman, N.M. & Istradefylline 6002-US-013 Study Group. (2008). Study of istradefylline in patients with Parkinson's disease on levodopa with motor fluctuations. *Movement disorders*, Vol.23, No.15, pp. 2177-2185
- Herranz, M. & Esteller, M. (2006). New therapeutic targets in cancer: the epigenetic connection. *Clinical & translational oncology*, Vol.8, No.4, pp. 242-249
- Illingworth, R.S. & Bird, A.P. (2009). CpG islands--'a rough guide'. *FEBS letters*, Vol.583, No.11, pp. 1713-1720

- Jones, P.A. (1999). The DNA methylation paradox. *Trends in genetics*, Vol.15, No.1, pp.34-37
- Kagan, B.L.; Sultzer, D.L.; Rosenlicht, N. & Gerner, R.H. (1990). Oral S-adenosylmethionine in depression: a randomized, double-blind, placebo-controlled trial. *The American journal of psychiatry*, Vol.147, No.5, pp. 591-595
- Kreth, S.; Ledderose, C.; Kaufmann, I.; Groeger, G. & Thiel, M. (2008). Differential expression of 5'-UTR splice variants of the adenosine A<sub>2A</sub> receptor gene in human granulocytes: identification, characterization, and functional impact on activation. *The FASEB journal*, Vol.22, No.9, pp. 3276-3286
- Ladd-Acosta, C.; Pevsner, J.; Sabunciyar, S.; Yolken, R.H.; Webster, M.J.; Dinkins, T.; Callinan, P.A.; Fan, J.B.; Potash, J.B. & Feinberg, A.P. (2007). DNA methylation signatures within the human brain. *American journal of human genetics*, Vol.81, No.6, pp. 1304-1315
- Le, F.; Townsend-Nicholson, A.; Baker, E.; Sutherland, G.R. & Schofield, P.R. (1996). Characterization and chromosomal localization of the human A<sub>2A</sub> adenosine receptor gene: ADORA2A. *Biochemical and biophysical research communications*, Vol.223, No.2, pp. 461-467
- Lewitt, P.A. (2008a). Levodopa for the treatment of Parkinson's disease. *The New England journal of medicine*, Vol.359, No.23, pp. 2468-2476
- LeWitt, P.A.; Guttman, M.; Tetrud, J.W.; Tuite, P.J.; Mori, A.; Chaikin, P.; Sussman, N.M. & 6002-US-005 Study Group. (2008b). Adenosine A<sub>2A</sub> receptor antagonist istradefylline (KW-6002) reduces "off" time in Parkinson's disease: a double-blind, randomized, multicenter clinical trial (6002-US-005). *Annals of neurology*, Vol.63, No.3, pp. 295-302
- Linden, J. (2001). Molecular approach to adenosine receptors: receptor-mediated mechanisms of tissue protection. *Annual review of pharmacology and toxicology*, Vol.41, pp. 775-787
- Linnebank, M.; Popp, J.; Smulders, Y.; Smith, D.; Semmler, A.; Farkas, M.; Kulic, L.; Cvetanovska, G.; Blom, H.; Stoffel-Wagner, B.; Kölsch, H.; Weller, M. & Jessen, F. (2010). S-adenosylmethionine is decreased in the cerebrospinal fluid of patients with Alzheimer's disease. *Neuro-degenerative diseases*, Vol.7, No.6, pp. 373-378
- Lipinski, J.F.; Cohen, B.M.; Frankenburg, F.; Tohen, M.; Wateraux, C.; Altesman, R.; Jones, B. & Harris, P. (1984). Open trial of S-adenosylmethionine for treatment of depression. *The American journal of psychiatry*, Vol.141, No.3, pp. 448-450
- Liu, L.; van Groen, T.; Kadish, I. & Tollefsbol, T.O. (2009). DNA methylation impacts on learning and memory in aging. *Neurobiology of aging*, Vol.30, No.4, pp.549-560
- Liu, X.X.; Wilson, K. & Charlton, C.G. (2000). Effects of L-dopa treatment on methylation in mouse brain: implications for the side effects of L-dopa. *Life sciences*, Vol.66, No.23, pp. 2277-2288
- Lu, S.C. (2000). S-Adenosylmethionine. *The international journal of biochemistry & cell biology*, Vol.32, No.4, pp. 391-395
- MacCollin, M.; Peterfreund, R.; MacDonald, M.; Fink, J.S. & Gusella, J. (1994). Mapping of a human A<sub>2A</sub> adenosine receptor (ADORA2) to chromosome 22. *Genomics*, Vol.20, No.2, pp. 332-333

- Masino, S.A.; Diao, L.; Illes, P.; Zahniser, N.R.; Larson, G.A.; Johansson, B.; Fredholm, B.B. & Dunwiddie, T.V. (2002). Modulation of hippocampal glutamatergic transmission by ATP is dependent on adenosine a(1) receptors. *The Journal of pharmacological and experimental therapeutics*, Vol.303, No.1, pp. 356-363
- Miller, J.W.; Selhub, J.; Nadeau, M.R.; Thomas, C.A.; Feldman, R.G. & Wolf, P.A. (2003). Effect of L-dopa on plasma homocysteine in PD patients: relationship to B-vitamin status. *Neurology*, Vol.60, No.7, pp. 1125-1129
- Mizuno, Y.; Hasegawa, K.; Kondo, T.; Kuno, S.; Yamamoto, M. & Japanese Istradefylline Study Group. (2010). Clinical efficacy of istradefylline (KW-6002) in Parkinson's disease: a randomized, controlled study. *Movement disorders*, Vol.25, No.10, pp. 1437-1443
- Morris, M.S. (2003). Homocysteine and Alzheimer's disease. *Lancet neurology*, Vol.2, No.7, pp. 425-428
- Morrison, L.D.; Smith, D.D. & Kish, S.J. (1996). Brain S-adenosylmethionine levels are severely decreased in Alzheimer's disease. *Journal of neurochemistry*, Vol.67, No.3, pp. 1328-1331
- Müller, T.; Voitalla, D.; Hauptmann, B.; Fowler, B. & Kuhn, W. (2001). Decrease of methionine and S-adenosylmethionine and increase of homocysteine in treated patients with Parkinson's disease. *Neuroscience letters*, Vol.308, No.1, pp. 54-56
- Müller, T.; Voitalla, D. & Kuhn, W. (2003). Benefit of folic acid supplementation in parkinsonian patients treated with levodopa. *Journal of neurology, neurosurgery, and psychiatry*, Vol.74, No.4, pp. 549
- Müller, T. & Kuhn, W. (2006). Tolcapone decreases plasma levels of S-adenosyl-L-homocysteine and homocysteine in treated Parkinson's disease patients. *European journal of clinical pharmacology*, Vol.62, No.6, pp. 447-450
- Müller, T. & Kuhn, W. (2009a). Homocysteine levels after acute levodopa intake in patients with Parkinson's disease. *Movement disorders*, Vol.24, No.9, pp. 1339-1343
- Müller, T. & Muhlack, S. (2009b) Peripheral COMT inhibition prevents levodopa associated homocysteine increase. *Journal of neural transmission*, Vol.116, No.10, pp. 1253-1256
- Nutt, J.G. (2008). Pharmacokinetics and pharmacodynamics of levodopa. *Movement disorders*, Vol.23, No.3, pp. S580-S584
- Obeid, R.; Schadt, A.; Dillmann, U.; Kostopoulos, P.; Fassbender, K. & Herrmann, W. (2009). Methylation status and neurodegenerative markers in Parkinson disease. *Clinical chemistry*, Vol.55, No.10, pp. 1852-1860
- Obeso, J.A.; Olanow, C.W. & Nutt, J.G. (2000). Levodopa motor complications in Parkinson's disease. *Trends in neurosciences*, Vol.23, No.10, pp. S2-S7
- Orru, M.; Bakešová, J.; Brugarolas, M.; Quiroz, C.; Beaumont, V.; Goldberg, S.R.; Lluís, C.; Cortés, A.; Franco, R.; Casadó, V.; Canela, E.I. & Ferré, S. (2011) Striatal pre- and post-synaptic profile of adenosine A(2A) receptor antagonists. *PLoS One*, Vol.6, No.1, pp. e16088
- O'Suilleabhain, P.E.; Sung, V.; Hernandez, C.; Lacritz, L.; Dewey, R.B. Jr; Bottiglieri, T. & Diaz-Arrastia, R. (2004). Elevated plasma homocysteine level in patients with Parkinson disease: motor, affective, and cognitive associations. *Archives of neurology*, Vol.61, No.6, pp. 865-868

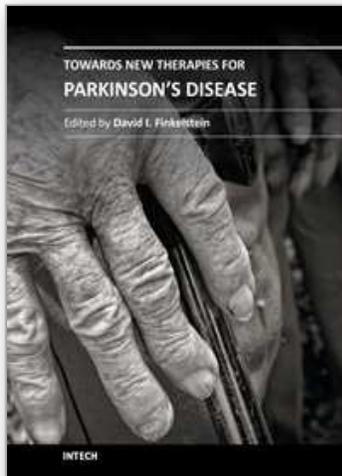
- Ohta, A. & Sitkovsky, M. (2001). Role of G-protein-coupled adenosine receptors in downregulation of inflammation and protection from tissue damage. *Nature*, Vol.414, No.6866, pp. 916-920
- Panza, F.; Frisardi, V.; Capurso, C.; D'Introno, A.; Colacicco, A.M.; Vendemiale, G.; Capurso, A. & Solfrizzi, V. (2009). Possible role of S-adenosylmethionine, S-adenosylhomocysteine, and polyunsaturated fatty acids in predementia syndromes and Alzheimer's disease. *Journal of Alzheimer's disease*, Vol.16, No.3, pp. 467-470
- Papakostas, G.I. (2009). Evidence for S-adenosyl-L-methionine (SAM-e) for the treatment of major depressive disorder. *The Journal of clinical psychiatry*, Vol.70, No.5, pp. 18-22
- Papakostas, G.I.; Mischoulon, D.; Shyu, I.; Alpert, J.E. & Fava, M. (2010). S-adenosyl methionine (SAME) augmentation of serotonin reuptake inhibitors for antidepressant nonresponders with major depressive disorder: a double-blind, randomized clinical trial. *The American journal of psychiatry*, Vol.167, No.8, pp. 942-948
- Pascale, R.M.; Marras, V.; Simile, M.M.; Daino, L.; Pinna, G.; Bennati, S.; Carta, M.; Seddaiu, M.A.; Massarelli, G. & Feo, F. (1992). Chemoprevention of rat liver carcinogenesis by S-adenosyl-L-methionine: a long-term study. *Cancer research*, Vol.52, No.18, pp. 4979-4986
- Peterfreund, R.A.; MacCollin, M.; Gusella, J. & Fink, J.S. (1996). Characterization and expression of the human A<sub>2A</sub> adenosine receptor gene. *Journal of neurochemistry*, Vol.66, No.1, pp. 362-368
- Pinna, A.; Corsi, C.; Carta, A.R.; Valentini, V.; Pedata, F. & Morelli, M. (2002). Modification of adenosine extracellular levels and adenosine A<sub>2A</sub> receptor mRNA by dopamine denervation. *European journal of pharmacology*, Vol.446, No.1-3, pp. 75-82
- Perez-Buira, S.; Barrachina, M.; Rodriguez, A.; Albasanz, J.L.; Martín, M. & Ferrer, I. (2007). Expression levels of adenosine receptors in hippocampus and frontal cortex in argyrophilic grain disease. *Neuroscience letters*, Vol.423, Vol.3, pp.194-199
- Portela, A. & Esteller, M. (2010). Epigenetic modifications and human disease. *Nature biotechnology*, Vol.28, No.10, pp.1057-1068
- Quadri, P.; Fragiaco, C.; Pezzati, R.; Zanda, E.; Forloni, G.; Tettamanti, M. & Lucca, U. (2004). Homocysteine, folate, and vitamin B-12 in mild cognitive impairment, Alzheimer disease, and vascular dementia. *The American journal of clinical nutrition*, Vol.80, No.1, pp. 114-122
- Quiroz, C.; Luján, R.; Uchigashima, M.; Simoes, A.P.; Lerner, T.N.; Borycz, J.; Kachroo, A.; Canas, P.M.; Orru, M.; Schwarzschild, M.A.; Rosin, D.L.; Kreitzer, A.C.; Cunha, R.A.; Watanabe, M. & Ferré, S. (2009). Key modulatory role of presynaptic adenosine A<sub>2A</sub> receptors in cortical neurotransmission to the striatal direct pathway. *ScientificWorldJournal*, No.9, pp. 1321-1344
- Ralevic, V. & Burnstock, G. (1998). Receptors for purines and pyrimidines. *Pharmacological reviews*, Vol.50, No.3, pp. 413-492
- Remington, R.; Chan, A.; Paskavitz, J. & Shea, T.B. (2009). Efficacy of a vitamin/nutriceutical formulation for moderate-stage to later-stage Alzheimer's disease: a placebo-controlled pilot study. *American journal of Alzheimer's disease and other dementias*, Vol.24, No.1, pp. 27-33

- Ribeiro, J.A.; Sebastião, A.M. & de Mendonça, A. (2002). Adenosine receptors in the nervous system: pathophysiological implications. *Progress in neurobiology*, Vol.68, No.6, pp. 377-392
- Rodrigues, R.J.; Alfaro, T.M.; Rebola, N.; Oliveira, C.R. & Cunha, R.A. (2005). Co-localization and functional interaction between adenosine A(2A) and metabotropic group 5 receptors in glutamatergic nerve terminals of the rat striatum. *Journal of neurochemistry*, Vol.92, No.3, pp. 433-441
- Rodríguez, A.; Martín, M.; Albasanz, J.L.; Barrachina, M.; Espinosa, J.C.; Torres, J.M. & Ferrer, I. (2006). Adenosine A1 receptor protein levels and activity is increased in the cerebral cortex in Creutzfeldt-Jakob disease and in bovine spongiform encephalopathy-infected bovine-PrP mice. *Journal of neuropathology and experimental neurology*, Vol.65, No.10, pp. 964-975
- Satoh, S.; Matsumura, H. & Hayaishi, O. (1998). Involvement of adenosine A2A receptor in sleep promotion. *European journal of pharmacology*, Vol.351, No.2, pp. 155-162
- Scarpa, S.; Fusco, A.; D'Anselmi, F. & Cavallaro, R.A. (2003). Presenilin 1 gene silencing by S-adenosylmethionine: a treatment for Alzheimer disease? *FEBS letters*, Vol.541, No.1-3, pp. 145-148
- Schiffmann, S.N.; Libert, F.; Vassart, G. & Vanderhaeghen, J.J. (1991). Distribution of adenosine A2 receptor mRNA in the human brain. *Neuroscience letters*, Vol.130, No.2, pp. 177-181
- Schiffmann, S.N.; Fisone, G.; Moresco, R.; Cunha, R.A. & Ferré, S. (2007). Adenosine A2A receptors and basal ganglia physiology. *Progress in neurobiology*, Vol.83, No.5, pp. 277-292
- Sebastião, A.M. & Ribeiro, J.A. (1996). Adenosine A2 receptor-mediated excitatory actions on the nervous system. *Progress in neurobiology*, Vol.48, No.3, pp. 167-189
- Seshadri, S.; Beiser, A.; Selhub, J.; Jacques, P.F.; Rosenberg, I.H.; D'Agostino, R.B.; Wilson, P.W. & Wolf, P.A. (2002). Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. *The New England journal of medicine*, Vol.346, No.7, pp. 476-483
- Shea, T.B. & Chan, A. (2008). S-adenosyl methionine: a natural therapeutic agent effective against multiple hallmarks and risk factors associated with Alzheimer's disease. *Journal of Alzheimer's disease*, Vol.13, No.1, pp.67-70
- Siegmund, K.D.; Connor, C.M.; Campan, M.; Long, T.I.; Weisenberger, D.J.; Biniszkiwicz, D.; Jaenisch, R.; Laird, P.W. & Akbarian, S. (2007). DNA methylation in the human cerebral cortex is dynamically regulated throughout the life span and involves differentiated neurons. *PLoS One*, Vol.2, No.9, pp. e895
- Stacy, M.; Silver, D.; Mendis, T.; Sutton, J.; Mori, A.; Chaikin, P. & Sussman, N.M. (2008). A 12-week, placebo-controlled study (6002-US-006) of istradefylline in Parkinson disease. *Neurology*, Vol.70, No.23, pp. 2233-2240
- Stone, T.W.; Ceruti, S. & Abbracchio, M.P. (2009). Adenosine receptors and neurological disease: neuroprotection and neurodegeneration. *Handbook of experimental pharmacology*, Vol.193, pp.535-587
- Tolosa, E.; Martí, M.J.; Valldeoriola, F. & Molinuevo, J.L. (1998). History of levodopa and dopamine agonists in Parkinson's disease treatment. *Neurology*, Vol.50, No.6 Suppl 6, pp. S2-S10

- Tomiyama, M.; Kimura, T.; Maeda, T.; Tanaka, H.; Kannari, K. & Baba, M. (2004). Upregulation of striatal adenosine A<sub>2A</sub> receptor mRNA in 6-hydroxydopamine-lesioned rats intermittently treated with L-DOPA. *Synapse*, Vol.52, No.3, pp. 218-222
- Tremolizzo, L.; Carboni, G.; Ruzicka, W.B.; Mitchell, C.P.; Sugaya, I.; Tueting, P.; Sharma, R.; Grayson, D.R.; Costa, E. & Guidotti, A. (2002). An epigenetic mouse model for molecular and behavioral neuropathologies related to schizophrenia vulnerability. *Proceeding of the National Academy of Sciences of the United States of America*, Vol.99, No.26, pp. 17095-17100
- Van Calker, D.; Müller, M. & Hamprecht, B. (1979). Adenosine regulates via two different types of receptors, the accumulation of cyclic AMP in cultured brain cells. *Journal of neurochemistry*, Vol.33, No.5, pp. 999-1005
- Varani, K.; Vincenzi, F.; Tosi, A.; Gessi, S.; Casetta, I.; Granieri, G.; Fazio, P.; Leung, E.; MacLennan, S.; Granieri, E. & Borea, P.A. (2010). A<sub>2A</sub> adenosine receptor overexpression and functionality, as well as TNF- $\alpha$  levels, correlate with motor symptoms in Parkinson's disease. *The FASEB journal*, Vol.24, No.2, pp.587-598
- Veldic, M.; Caruncho, H.J.; Liu, W.S.; Davis, J.; Satta, R.; Grayson, D.R.; Guidotti, A. & Costa, E. (2004) DNA-methyltransferase 1 mRNA is selectively overexpressed in telencephalic GABAergic interneurons of schizophrenia brains. *Proceeding of the National Academy of Sciences of the United States of America*, Vol.101, No.1, pp. 348-353
- Veldic, M.; Guidotti, A.; Maloku, E.; Davis, J.M. & Costa, E. (2005). In psychosis, cortical interneurons overexpress DNA-methyltransferase 1. *Proceeding of the National Academy of Sciences of the United States of America*, Vol.102, No.6, pp. 2152-2157
- Vitvitsky, V.; Thomas, M.; Ghorpade, A.; Gendelman, H.E. & Banerjee, R. (2006). A functional transsulfuration pathway in the brain links to glutathione homeostasis. *The Journal of biological chemistry*, Vol. 281, No.47, pp. 35785-35793
- Wang, S.C.; Oelze, B. & Schumacher, A. (2008). Age-specific epigenetic drift in late-onset Alzheimer's disease. *PLoS One*, Vol.3, No.7, pp. e2698
- Waterland, R.A. & Jirtle, R.L. (2003). Transposable elements: targets for early nutritional effects on epigenetic gene regulation. *Molecular and cellular biology*, Vol.23, No.15, pp. 5293-5300
- Woitalla, D.; Kuhn, W. & Müller, T. (2004). MTHFR C677T polymorphism, folic acid and hyperhomocysteinemia in levodopa treated patients with Parkinson's disease. *Journal of neural transmission*, Vol.68, pp. 15-20
- Yasui, K.; Kowa, H.; Nakaso, K.; Takeshima, T. & Nakashima, K. (2000). Plasma homocysteine and MTHFR C677T genotype in levodopa-treated patients with PD. *Neurology*, Vol.55, No.3, pp. 437-440
- Yu, L.; Frith, M.C.; Suzuki, Y.; Peterfreund, R.A.; Gearan, T.; Sugano, S.; Schwarzschild, M.A.; Weng, Z.; Fink, J.S. & Chen, J.F. (2004). Characterization of genomic organization of the adenosine A<sub>2A</sub> receptor gene by molecular and bioinformatics analyses. *Brain research*, Vol.1000, No.1-2, pp. 156-173
- Zoccolella, S.; Lamberti, P.; Iliceto, G.; Dell'Aquila, C.; Diroma, C.; Fraddosio, A.; Lamberti, S.V.; Armenise, E.; Defazio, G.; de Mari, M. & Livrea, P. (2006). Elevated plasma

- homocysteine levels in L-dopa-treated Parkinson's disease patients with dyskinesias. *Clinical chemistry and laboratory medicine*, Vol.44, No.7, pp. 863-866
- Zoccolella, S.; Iliceto, G.; deMari, M.; Livrea, P. & Lamberti, P. (2007). Management of L-Dopa related hyperhomocysteinemia: catechol-O-methyltransferase (COMT) inhibitors or B vitamins? Results from a review. *Clinical chemistry and laboratory medicine*, Vol.45, No.12, pp. 1607-1613
- Zoccolella, S.; dell'Aquila, C.; Abruzzese, G.; Antonini, A.; Bonuccelli, U.; Canesi, M.; Cristina, S.; Marchese, R.; Pacchetti, C.; Zagaglia, R.; Logroscino, G.; Defazio, G.; Lamberti, P. & Livrea, P. (2009). Hyperhomocysteinemia in levodopa-treated patients with Parkinson's disease dementia. *Movement disorders*, Vol.24, No.7, pp. 1028-1033
- Zoccolella, S.; Lamberti, S.V.; Iliceto, G.; Santamato, A.; Lamberti, P. & Logroscino, G. (2010). Hyperhomocysteinemia in L-dopa treated patients with Parkinson's disease: potential implications in cognitive dysfunction and dementia? *Current medicinal chemistry*, Vol.17, No.28, pp. 3253-3261

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## **Towards New Therapies for Parkinson's Disease**

Edited by Prof. David Finkelstein

ISBN 978-953-307-463-4

Hard cover, 396 pages

**Publisher** InTech

**Published online** 02, November, 2011

**Published in print edition** November, 2011

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  $\alpha$ -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.

### **How to reference**

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Marta Barrachina, Mairena Marín, Francisco Ciruela and Isidre Ferrer (2011). Epigenetic Modulation of Adenosine A2A Receptor: A Putative Therapeutical Tool for the Treatment of Parkinson's Disease, Towards New Therapies for Parkinson's Disease, Prof. David Finkelstein (Ed.), ISBN: 978-953-307-463-4, InTech, Available from: <http://www.intechopen.com/books/towards-new-therapies-for-parkinson-s-disease/epigenetic-modulation-of-adenosine-a2a-receptor-a-putative-therapeutical-tool-for-the-treatment-of-p>

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