NEURAL REGENERATION RESEARCH
February 2015, Volume 10, Issue 2
www.nrronline.org

PERSPECTIVE

The seeming paradox of adenosine receptors as targets for the treatment of Alzheimer's disease: agonists or antagonists?

Alzheimer's disease (AD) is the most common neurodegenerative disorder, and its incidence is relatively high among elderly people, affecting about 1–2% of the population between 60–65 years old and rising dramatically (about 30%) in people aged 80 years or older (Selkoe, 2002). Nowadays, considering the increasing mean lifespan of populations in developed countries, the disease is becoming more and more a health concern, and the search for an effective cure has turned into"a real need". Common signs of AD are difficult to be recognized at the onset of the pathology, primarily because endogenous mechanisms tend to compensate the initial neurodegenerative process. However, when symptoms appear, structural brain damage is already extended and is accompanied by the progressive and relentless deterioration of cognitive functions, which lastly culminate in severe memory loss and dementia. From a biochemical point of view, the typical neuropathological hallmarks of AD range from synaptic/neuronal loss in several areas of the brain, such as the neocortex and hippocampus, to the formation of senile plaques, mainly composed of the neurotoxic amyloid-β peptide (Aβ). According to the well-consolidated "amyloidogenic cascade hypothesis", the pathogenetic mechanism that drives cognitive decline in AD seems to be triggered by the aberrant processing of the amyloid precursor protein (APP) by β-secretases, that diverts from the physiological cleavage of APP, and that leads to the anomalous accumulation of the noxious Aβ peptide within the brain, culminating in the formation of aggregates within the surrounding brain parenchyma and progressive neuronal death. However, while the exact causative factors that lead to the abnormal Aβ processing in AD remain largely unknown, unanimous consensus claiming that environmental agents act as potential contributing factors to aggravate AD pathogenesis seems to have been reached. Indeed, evidences from our laboratories have strongly suggested that exposure to a broadly used metal, aluminum, may actually promote and (maybe) accelerate the amyloidogenic pathway by increasing oxidative stress mechanisms, reducing antioxidant defense response, and finally by affecting the expression of AD- and stress-related molecules, thereby speeding up the overall degenerative process in AD (Castorina et al., 2010; Giunta et al., 2014). As said, it is therefore of paramount importance to discover new effective drugs able to address this unmet medical need. For the purpose, at least two main routes are available: (1) identify new potential targets to develop drugs able to slow down or arrest disease progression; (2) shed more light into those "old" molecules that have demonstrated proven efficacy in ameliorating many aspects of cognitive deterioration in a number of neurodegenerative conditions but that have been "left apart" because scientific evidences were apparently controversial. Since the first option may appear the most desirable, many would think this choice is the most appropriate. Unfortunately it is not, and on the contrary, it is the slowest track and the less likely to give the expected results for many reasons. For instance, if an effective molecular target is identified, the steps that would lead to the production of a readily available drug to test into clinical trials are really tortuous, and often not feasible. According to a study conducted by Enna and Williams (2009), only very few high-affinity ligands for potentially attractive molecular targets progress to further evaluation as future drug candidates, and most of these "fortunate ligands" will be even reduced in number after undergoing a series of necessary screening tests. In other cases, molecules directed to specific targets are simply difficult or even impossible to be synthesized as administrable drugs or produce a series of severe side effects. Therefore, despite being a challenging route, the second option to revisit "old drugs" to produce new and more selective drugs remains the most feasible.

Many epidemiological studies have shown that the habitual consumption of moderate quantities of the worldwide consumed psychoactive drug caffeine through drinking diet produces long-lasting benefits to memory function in both healthy and diseased brains. Such benefits include reduced memory decline caused by physiological aging but also reduced risk to develop dementia and AD, suggesting its potential therapeutic use. But where do caffeine beneficial effects arise from?

According to current knowledge, the mechanisms of action of the methylxanthine caffeine (1,3,7-trimethylxanthine) to trigger ameliorative effects in the brain seem to be related to the structural similarities between the compound itself and an endogenously produced molecule known as adenosine (**Figure 1**). Adenosine is a purine nucleoside composed of a molecule of adenine attached to a ribose sugar molecule (ribofuranose) moiety *via* a β-N_9-glycosidic bond. It is known to play key roles in energy transfer and as signaling molecule when it is in the form of adenosine triphosphate (ATP) and adenosine diphosphate (ADP), and acts as a second messenger in signal transduction mechanisms when in the form of cyclic adenosine monophosphate (cAMP). It is also a neuromodulator, believed to play a role in promoting sleep and suppressing arousal. Adenosine activity is mediated by four different adenosine receptor subtypes (A_1R, $A_{2A}R$,

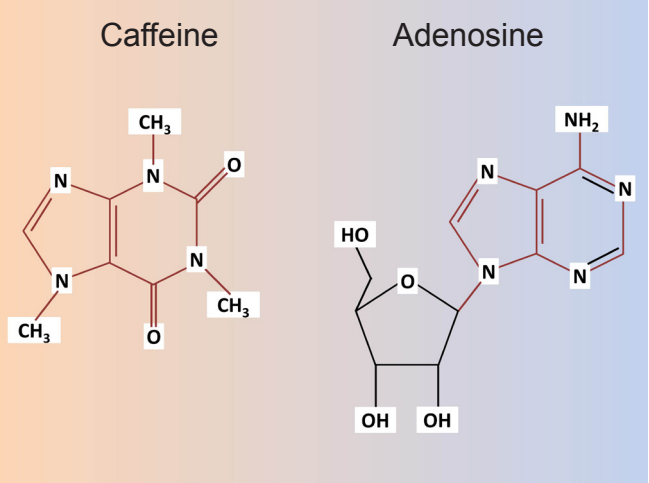

Figure 1 Chemical structure of caffeine and adenosine.
Depicted are the chemical structures of the widely used drug "caffeine" and the endogenously produced nucleoside "adenosine" for comparison. Structural similarities are highlighted in red.

$A_{2B}R$ and A_3R) (Haskó et al., 2007), of which the A_1R and $A_{2A}R$ show the highest density in the brain. Binding of adenosine to each of its receptor subtypes produces a constellation of responses, especially at synapses, although these vary a lot depending on whether the neuron is active or not, healthy or injured. It is common belief that the endogenous purine nucleoside, released by neurons in resting state (when synaptic activity is not engaged), binds to A_1Rs to trigger an inhibitory function that promotes energy saving, whereas in stimulated/activated neurons $A_{2A}R$ are recruited to counteract A_1R-mediated inhibitory function on synapses, thereby promoting an increase in synaptic efficiency. Therefore, the homeostatic control on energy metabolism and neuronal activity by regulating adenosine release seems crucial to regulate normal brain physiology. On the other hand, caffeine acts as a non-selective competitive agonist of both A_1Rs and $A_{2A}Rs$. Indeed, caffeine binding to A_1Rs and $A_{2A}Rs$ competes with adenosine, thereby reducing the possibility of the nucleoside to bind to its receptors to determine an inhibitory function on neurons. The resultant effect is increased neuronal activation. Accordingly, administration of caffeine causes many positive central nervous system (CNS) effects, including increased attention, memory and arousal state. The Food and Drug Administration recognized caffeine as being generally safe, but it should be mentioned that it is not completely exempt from some minor unwanted peripheral side effects, such as tachycardia and insomnia.

In relationship to AD, several studies suggest that adenosine receptors change their pattern of localization and density in affected brain regions. Post-mortem analyses of the frontal cortex of AD patients showed that the total number and levels of A_1R and $A_{2A}R$ are significantly increased in either early or advanced stages of the disease (Albasanz et al., 2008). Pre-clinical studies using mice models of AD show that chronic consumption of caffeine is prophylactic against Aβ plaque development and associated cognitive deficits, but the most exciting evidence comes from a study showing that $A_{2A}R$ antagonists or caffeine can even revert memory impairment in different models with overt memory decline (Laurent et al., 2014), implying that most of the memory-recovering effects should be attributed to $A_{2A}R$ blockade.

Of interest, several other studies have demonstrated that targeting adenosine receptors using specific agonists

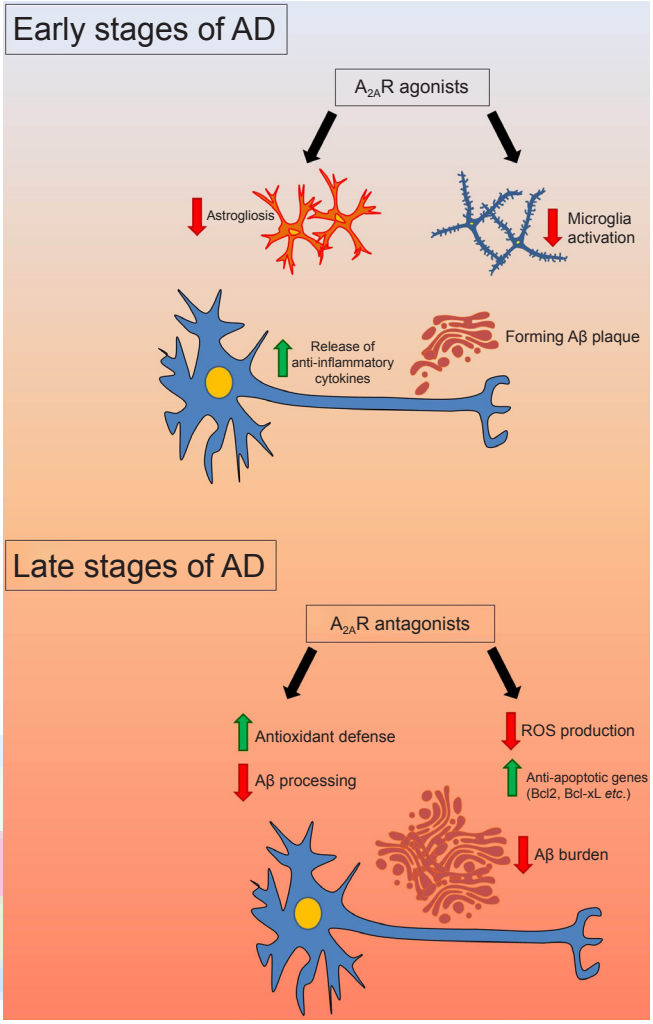

Figure 2 Schematic model to explain the seemingly paradoxical use of adenosine receptor agonists or antagonists for the treatment of Alzheimer's disease (AD).
During the initial phases of the disease, neuroinflammation appears to be a predominant event, involving microglia activation, astrogliosis and recruitment of peripheral macrophages through the release of pro-inflammatory cytokines. Adenosine receptor subtype $A_{2A}R$ agonists trigger anti-inflammatory responses that may counteract AD progression (upper panel). In overt AD, oxidative mechanisms prevail on neuroinflammation, thus promoting amyloid-β (Aβ) processing. $A_{2A}R$ antagonists possess antioxidant and anti-apoptotic activities, and reduce-(Aβ) burden by downregulating genes involved in amyloid precursor protein cleavage (lower panel).

instead of antagonists may also provide significant neuroprotective effects on various models of neurodegenerative diseases, possibly by interfering with excitatory neurotransmitter release, apoptotic mechanisms and more importantly, by reducing local inflammatory responses. It is now well-established that especially during the earliest phases of AD, inflammation is a predominant event (recently reviewed by Subash et al. (2014)), and that activation of the adenosine system through $A_{2A}R$ agonism can lead to the down-regulation of the inflammatory response (Csóka and Haskó, 2011) as well as the prevention of Aβ-induced synaptotoxicity by promoting the release of interleukin-10 (IL-10), the major anti-inflammatory cytokine, by resident cells. Another critical aspect pointing to the use of adenosine receptor agonists resides on the fact that AD patients show impaired signaling by the neurotrophin molecule brain derived neutrophic factor (BDNF), and that $A_{2A}R$ activation is critical for both BDNF-dependent and -independent hippocampal synaptic transmission, plasticity and LTP. It is thus important to understand that data obtained from the several studies attempting to define a strategy to treat the disease should be interpreted with care. Indeed, it looks like the apparently sharp contrast existing between the two research strands relies on specific aspects of AD development, including: (1) the initial phase in which persistent brain inflammation at the site of injury (where plaques develop) is observed; (2) a late phase in which Aβ aggregates succeed to invade and kill neuronal cells and surrounding glia by inducing reactive oxygen species production and activation of the apoptotic machinery (**Figure 2**). Based on the "bidirectional effect" of $A_{2A}R$ activation and inhibition proposed by Dai and Zhou (2011), different stages of the pathological process as well as the route of administration may significantly impact the efficacy of treatment with either agonist or antagonists for adenosine receptors. The apparently paradoxical use of two oppositely acting ligands to treat the same neurodegenerative condition suggests that factors such as dosage, drug delivery method, state of disease progression and extracellular concentrations of potential excitotoxic transmitters might determine similar cellular responses to opposite pharmacological treatments. More specifically, it seems that the protection afforded by $A_{2A}R$ agonists against AD is transient but effective during the earliest phases of the disease, and it is mainly achieved through a stimulatory effect on the release and production of anti-inflammatory cytokines by resident glial and peripheral immune cells. Conversely, both prophylactic and long-term neuroprotective effects of caffeine and/or $A_{2A}R$ antagonists are for the most attributable to inhibition of reactive oxygen species activity, tau pathology and Aβ production by neuronal cells.

We may conclude that the protection offered by adenosine receptor agonists could mostly be beneficial in the earliest stages of the disease to prevent/reduce the deteriorating effects caused by inflammation and cytokine release by reactive astrocytes and microglia and by reducing neuronal activity state in the attempt to preserve cell viability, whereas adenosine antagonists (in particular $A_{2A}R$ antagonists), despite their ability to potentially prevent AD onset, would mostly affect the late phases of disease progression. It is thus important to define how specific substrates of adenosine receptors are differentially regulated at the different stages of AD development. As a consequence, in the light of these evidences, it is suggested that a correct therapeutic strategy should include a timely and accurate evaluation of disease stage/progression prior to selecting the most appropriate drug regimen.

Rubina Marzagalli, Alessandro Castorina*

Department of Biomedical Sciences and Biotechnologies, Section of Human Anatomy and Histology, University of Catania, Italy

***Correspondence to:** *Alessandro Castorina, M.S., Ph.D., alecasto@unict.it.*
***Accepted:** 2014-12-16*
***doi:**10.4103/1673-5374.152370* ***http**://www.nrronline.org/*
Marzagalli R, Castorina A (2015) The seeming paradox of adenosine receptors as targets for the treatment of Alzheimer's disease: agonists or antagonists? Neural Regen Res 10(2):205-207.

References

Albasanz JL, Perez S, Barrachina M, Ferrer I, Martín M (2008) Up-regulation of adenosine receptors in the frontal cortex in Alzheimer's disease. Brain Pathol 18:211-219.

Castorina A, Tiralongo A, Giunta S, Carnazza ML, Scapagnini G, D'Agata V (2010) Early effects of aluminum chloride on beta-secretase mRNA expression in a neuronal model of beta-amyloid toxicity. Cell Biol Toxicol 26:367-377.

Csóka B, Haskó G (2011) Adenosine, inflammation pathways and therapeutic challenges. Joint Bone Spine 78:4-6.

Dai SS, Zhou YG (2011) Adenosine 2A receptor: a crucial neuromodulator with bidirectional effect in neuroinflammation and brain injury. Rev Neurosci 22:231-239.

Enna SJ, Williams M (2009) Challenges in the search for drugs to treat central nervous system disorders. J Pharmacol Exp Ther 329:404-411.

Giunta S, Andriolo V, Castorina A (2014) Dual blockade of the A1 and A2A adenosine receptor prevents amyloid beta toxicity in neuroblastoma cells exposed to aluminum chloride. Int J Biochem Cell Biol 54:122-136.

Haskó G, Pacher P, Deitch EA, Vizi ES (2007) Shaping of monocyte and macrophage function by adenosine receptors. Pharmacol Ther 113:264-275.

Laurent C, Eddarkaoui S, Derisbourg M, Leboucher A, Demeyer D, Carrier S, Schneider M, Hamdane M, Müller CE, Buée L, Blum D (2014) Beneficial effects of caffeine in a transgenic model of Alzheimer's disease-like tau pathology. Neurobiol Aging 35:2079-2090.

Selkoe DJ (2002) Alzheimer's disease is a synaptic failure. Science 298:789-791.

Subash S, Essa MM, Al-Adawi S, Memon MA, Manivasagam T, Akbar M (2014) Neuroprotective effects of berry fruits on neurodegenerative diseases. Neural Regen Res 9:1557-1566.