Chapter 15
The Adenosine Receptor: A Homeostatic Neuromodulator for Fine-Tuning Control of Cognition

Jiang-Fan Chen

Abstract There is a convergence of neurochemical studies showing the dual roles of neuromodulation and homeostatic function by adenosine receptors (AR), with animal studies demonstrating the strong pro-cognitive impact upon AR antagonism in healthy and diseased brains, with the epidemiological evidence in support of caffeine and AR drugs used for the therapeutic modulation of cognition. This perspective led to the proposal that the adenosine and AR may uniquely position to modulate cognitive behaviors in normal and disease conditions. This review first describes the ability of AR to integrate dopamine and glutamate signaling and to modulate synaptic plasticity by acting through the inhibitory A_1 and facilitating A_{2A} receptors ($A_{2A}R$). It is followed by the discussion on the animal studies demonstrating the strong pro-cognitive effects of AR (mainly the A_{2A} receptor) antagonism on a variety of cognitive behaviors. These studies reveal several novel insights into the mechanism underlying AR control of cognition: temporally precise interaction of adenosine with dopamine and glutamate signaling at the striatum, striatopallidal A_{2A}Rs function as a common "break" mechanism to constrain cognition, and selective modulation of distinct phases of working memory information processing. We further describe the evidence for the aberrantly increased adenosine-AR signaling under pathological conditions. Accordingly, blocking the aberrant AR signaling reverses cognitive impairments in animal models of neurodegenerative disorders. AR modification of neurodegenerative proteins (including α-synuclein, β-amyloid, and phosphorylation of Tau) and neuroprotection against synaptic loss are discussed as the potential mechanisms underlying AR control of cognitive deficits. Last, translational potential of $A_{2A}R$ antagonists and caffeine for cognitive improvement is highlighted with non-human primate studies and epidemiological findings. As caffeine is regularly consumed by >50% world population and $A_{2A}R$ antagonists are in phase III clinical trials for Parkinson's disease with noted safety profiles, this convergence of molecular, animal, and epidemiological evidence supporting AR control of cognition will

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stimulate necessary clinical investigations to explore AR-targeting drugs as a novel strategy to ameliorate cognitive deficits in neuropsychiatric disorders.

Keywords Adenosine receptors · Cognition modulation · A_1R antagonism · $A_{2A}R$ antagonism · Neuropsychiatric disorders · Caffeine

15.1 Adenosine Acts as a Dual Controller of Homeostatic Metabolism and Neuromodulatory Function in the Brain

Adenosine has been postulated as a homeostatic regulator of metabolism in cells throughout the body. The basal level of adenosine is driven mainly by metabolic homeostasis and is apparently mostly independent of nerve activity. Under physiological conditions, the constant presence of a finite concentration of adenosine (in the range of ~30–300 nM) inside the cell (Ballarin et al. 1991) is ensured by the bidirectional enzyme activities of adenosine kinase and S-adenosylhomocysteine hydrolase (for generating adenosine by hydrolysis of adenosine monophosphate (AMP) or S-adenosylhomocysteine, respectively) (Fredholm 2007). Because of the presence of the efficient equilibrative purine transporters in all cells, the finite concentration of intracellular adenosine ensures that there is also a substantial extracellular concentration of adenosine (King et al. 2006), which is sufficient to active evolutionarily conserved adenosine receptors that are present on most, if not all, cells. In addition, extracellular adenosine is also formed by a series of ectoenzymes on the cell surface by the conversion of ATP to ADP and then to AMP (via many different ectoenzymes, especially CD39) (Yegutkin 2008) and then from AMP to adenosine (only via ecto-5′ nucleotidase CD73 in the brain) (Resta et al. 1998). Extracellular ATP can be generated not only by controlled co-release from the storage vesicles together with other neurotransmitters from the nerve terminals and uncontrolled leakage from necrotic cells (Eltzschig 2009) but also from the inflammatory cells or vascular endothelium through connexin hemichannels and channels such as P2X7 receptors (Chen et al. 2006; Linden 2006; Faigle et al. 2008) and also from various cells by a “kiss-and-run” mechanism (MacDonald et al. 2006), and lysosome exocytosis (Zhang et al. 2007). Thus, adenosine acts as a dual controller of a homeostatic regulator of metabolic activity by its paracrine signaling ability in all eukaryotic cells and of a specific neuromodulator in the brain by controlling neuronal excitability, the release of various neurotransmitters, and modulation of synaptic plasticity, neuroinflammation and cell death (Sebastiao and Ribeiro 1996). The adenosine control of neuronal function is thus intrinsically linked with its coordinate metabolic activity in the neuron, making it difficult to disentangle the dual roles of adenosine in the brain.

Extracellular adenosine reacts with one of the four adenosine receptors, namely, A_1, A_{2A}, A_{2B}, and A_3 (Fredholm et al. 2011). When they are expressed at the same

level (~200,000 receptors/cell), adenosine, under basal physiologic conditions, is sufficient and equally potent at A_1, A_{2A}, and A_3 receptors, whereas A_{2B} receptor is activated at higher levels of adenosine. Brain expression of the A_1 and A_{2A} receptors is significantly higher than the other two receptors (Fredholm et al. 2011), and adenosine mainly acts through inhibitory A_1R and facilitatory $A_{2A}R$ to fine-tune the brain neurotransmission (Fredholm et al. 2005a).

Adenosine A_1 receptor (A_1R): The A_1R is a Gi-protein-coupled receptor (van Calker et al. 1978; Londos et al. 1980) that is widely and abundantly expressed throughout the brain (Reppert et al. 1991; Dixon et al. 1996). The A_1R controls synaptic transmission by the presynaptic inhibition of a variety of neurotransmitters (particularly excitatory neurotransmitters such as glutamate) (Dunwiddie and Fredholm 1997; Dunwiddie and Masino 2001; Ribeiro et al. 2002) and by postsynaptic suppression of N-type calcium channels and NMDA receptors (Dunwiddie and Masino 2001; Ribeiro et al. 2002; Scanziani et al. 1992) and by nonsynaptic activation of inwardly rectifying K^+ channels (GIRKs) (Kim and Johnston 2015) and hyperpolarization of the resting membrane potential (Kirsch et al. 1990). Thus, the neuronal excitability and control of the "basal" synaptic transmission are primarily regulated by the A_1R activation presynaptically and postsynaptically as well as nonsynaptically (Wan et al. 1999).

Adenosine A_{2A} receptor ($A_{2A}R$): $A_{2A}Rs$ are highly enriched in the striatum where the expression is mostly localized to striatopallidal medium spiny neurons of the striatopallidal pathway (Fink et al. 1992; Schiffmann and Vanderhaeghen 1993). In the striatopallidal neurons, $A_{2A}Rs$ co-localize and interact with striatal dopamine D_2 receptors (D_2Rs) (Canals et al. 2003; Hillion et al. 2002; Fuxe et al. 2003) or N-methyl-D-aspartate receptors (NMDARs) (Gerevich et al. 2002; Wirkner et al. 2000) in an *antagonistic* manner, as well as with metabotropic glutamate 5 receptors ($mGlu_5Rs$) (Ferre et al. 2002; Coccurello et al. 2004; Kachroo et al. 2005), or cannabinoid CB_1 receptors (CB_1Rs) (Lerner et al. 2010; Ferre et al. 2010) in a *synergistic* manner. In particular, activation of the striatopallidal $A_{2A}Rs$, likely through the $A_{2A}R$-D_2R heterodimer, inhibits the D_2R binding and antagonizes the D_2R-mediated inhibition of GABA release (Mori and Shindou 2003), DARPP-32 phosphorylation (Shen et al. 2013), and c-Fos expression and inhibits NMDA current in the striatal neurons (Gerevich et al. 2002; Wirkner et al. 2000) as well as D_2R-mediated behaviors (Ferre et al. 1997; Ongini and Fredholm 1996). $A_{2A}Rs$ also modulate brain-derived neurotrophic factor (BDNF) function in the striatum by providing a permissive effect on BDNF release and by the intracellular transactivation of TrkB receptor (Sebastiao and Ribeiro 1996, 2000; Tebano et al. 2008). In CA1 region of the hippocampus, $A_{2A}R$ activity also exerts a permissive effect on the theta burst stimulation (TBS)-induced long-term potentiation with a concurrent increase in ERK1/2 activation, suggesting a possible tripartite A_{2A}, mGlu5, and NMDAR complex (Krania et al. 2018). Cortical $A_{2A}Rs$ located at corticostriatal projections (47, 48) modulate glutamate release (Rosin et al. 2003; Rebola et al. 2005a) to excite this synaptic transmission in the striatal neurons by locally shutting down the A_1R-mediated inhibition (Ciruela et al. 2006; Lopes et al. 1999a). Thus, while A_1R activation plays a prominent inhibitory role in the control of "basal" synaptic

transmission, A_{2A}Rs exert a limited effect on this but may have a facilitating role in controlling local synaptic plasticity (Gomes et al. 2011) (see below).

15.2 Coordinated Glial-Derived Adenosine for A_1R Global Inhibition and Neuronal-Derived Adenosine for Local A_{2A}R Activation

In the brain, extracellular adenosine might originate from neurons (both from nerve terminals and postsynaptic components) and surrounding non-neuronal cells such as glial cells (Halassa et al. 2007, 2009). As a neuromodulator, adenosine generated from different sources may preferentially act at different ARs to exert different control of synaptic plasticity. Indeed, early findings indicate that different sources of adenosine activate A_1R and A_{2A}R (Cunha et al. 1996) and that A_{2A}Rs are selectively activated upon extracellular catabolism by ecto-nucleotidases of ATP (Cunha et al. 1996; Rebola et al. 2008). Several studies have recently demonstrated a selective association of CD73-mediated formation of ATP-derived adenosine with the activation of facilitatory A_{2A}R in the brain (Fredholm et al. 2005a, b). This view is supported by our recent finding that CD73 and A_{2A}R co-localize (Ena et al. 2013) and are physically associated (Augusto et al. 2013) in the striatopallidal neurons and that CD73 provides the particular pool of extracellular adenosine selectively responsible for activating striatal A_{2A}R (Cunha 2001). This functional association between CD73 activity and the activation of striatal A_{2A}R is validated by the abolishment of ex vivo effect (i.e., cAMP formation) as well as in vivo effect (hypolocomotor) of a prodrug for A_{2A}R agonism either by CD73 knockout or by A_{2A}R knockout (Augusto et al. 2013). On the other hand, A_1R activation depends on the tissue workload (Cunha 2001), and the activity-dependent metabolic control of adenosine kinase is postulated to produce a direct outflow of adenosine for the activation of A_1R (Boison 2011; Diogenes et al. 2014; Brundege and Dunwiddie 1998). However, both astrocytes (Halassa et al. 2009; Schmitt et al. 2012) and postsynaptic neuronal components involve the vesicular nucleotide transport (VNUT) (Larsson et al. 2012; Lovatt et al. 2012) and may also be coupled to the activation of A1R.

This selective activation of the A_{2A}R by ATP-derived, CD73-mediated adenosine and activation of the A_1R by the activity-dependent metabolic control of adenosine kinase led to the proposal of a nonsynaptic transmission of adenosine to understand the differential activation of the inhibitory A_1R and facilitatory A_{2A}R according to the functional needs of neuronal circuits (Cunha 2008a). In this proposal, astrocyte-derived adenosine acts at the A_1R to produce global hetero-synaptic inhibition through astrocytic-driven volume transmission, while neuron-derived adenosine – via ATP conversion to adenosine by CD73 – acts at the A_{2A}R to exert local facilitation of plasticity (Gomes et al. 2011), leading to the local increase of a signal to noise ratio for the information processing in the brain (Gomes et al. 2011). As such, adenosine is critical for balancing inhibition and excitation toward homeostasis and in setting the stage for adenosine-mediated meta-plasticity (Dias et al. 2013). The

homeostatic and neuromodulatory control of neuronal processes underlies the ability of adenosine to regulate cognition because adenosine kinase (ADK)-mediated adenosine homeostatic function is necessary and permissive to synaptic actions of adenosine (Diogenes et al. 2014). Hence, mice with a conditional knockout or a brain-specific deletion of Adk ($Adk^{\Delta brain}$) develop seizures and cognitive deficits with increased basal synaptic transmission and enhanced $A_{2A}R$-dependent synaptic plasticity (Sandau et al. 2016).

15.3 A_1 and A_{2A} Receptor Modulation of Synaptic Plasticity Underlies Cognitive Control

Hebbian forms of synaptic plasticity, such as long-term potentiation (LTP) and long-term depression (LTD), are fundamental to associated learning and thought to form the cellular correlates of learning and memory. The homeostatic function of adenosine may provide the permissive condition to set the stage for Hebbian forms of plasticity (Dias et al. 2013). By the control of multiple neurotransmitter release and glutamate, dopamine, and BDNF signaling and by controlling neuronal excitability in the brain (Ribeiro 1999), ARs play a critical role in modulation of Hebbian plasticity in various brain regions (de Mendonca and Ribeiro 1997), including thalamocortical project (Blundon et al. 2011), somatosensory cortex (Marquez-Ruiz et al. 2012), hippocampus (CA3-CA1 synapse) (Rebola et al. 2008), corticostriatal projections (Shen et al. 2008b), hypothalamus (Xia et al. 2009), and neuronal muscle junction (Todd et al. 2010) (for review see Dias et al. 2013). Adenosine action at inhibitory A_1Rs and excitatory $A_{2A}Rs$ to modulate synaptic plasticity (e.g., LTP and LTD) in the brain underlies AR control of learning and memory. The precise contribution of A_1Rs and $A_{2A}Rs$ to adenosine regulation of synaptic plasticity in different brain regions, however, remains to be established.

15.3.1 A_1 Receptor Modulation of Synaptic Plasticity in Different Brain Regions

Despite the consistent inhibitory effect of the A_1R on glutamatergic transmission in the brain, studies with pharmacological and genetic manipulations of the A_1R have not produced consistent results on the A_1R control of synaptic plasticity in various brain regions. In the hippocampus, inactivation of A_1Rs can selectively augment mossy fiber basal transmission but attenuate both short-term plasticity (e.g., frequency facilitation and paired pulse facilitation) and LTP at this synapse (Moore et al. 2003). The A_1R activation via G protein-activated inwardly rectifying K(+) (GIRK) current in the hippocampus contributes to depotentiation of the previously potentiated LTP at Schaffer collateral synapses (Chung et al. 2009). However, local activation of A_1Rs impairs paired pulse facilitation but is not critical neither to the basal release probability and plasticity at mossy fiber synapses (Kukley et al. 2005)

nor LTD at the Schaffer collateral-CA1 pathway (Gimenez-Llort et al. 2005). In the striatum, A_1R inactivation has been shown to either abolish NMDAR-triggered LTD (Schotanus et al. 2006) and block short-term depression or have no effect on LTD at these synapses (Lovinger and Choi 1995). In cerebellar Purkinje cells, A_1Rs co-localize and form a heterodimeric complex with type-1 metabotropic glutamate receptor (mGluR1), and activation of the A_1R blocks mGluR1-mediated LTD (*glu-LTD*) (Kamikubo et al. 2013). In developing neocortex, local activation of A_1Rs presynaptically is critical to development shift in the release probability at synapses and potentially in long-term synaptic plasticity (Kerr et al. 2013). Additional studies are required to clarify the exact role of A_1R modulation of synaptic plasticity in various brain regions relevant to cognition.

15.3.2 Brain A_{2A} Receptors Modulate Synaptic Plasticity by Integrating Dopamine and Glutamate Signaling

The $A_{2A}R$, a G protein-coupled receptor, is highly enriched in striatopallidal neurons (Scanziani et al. 1992; Kim and Johnston 2015) where $A_{2A}Rs$ interact (possibly through heterodimerization) antagonistically with D_2Rs (Canals et al. 2003; Hillion et al. 2002; Fuxe et al. 2003) and NMDA receptors (Gerevich et al. 2002; Higley and Sabatini 2010) and synergistically with metabotropic glutamate receptor 5 (mGluR5) (Ferre et al. 2002; Coccurello et al. 2004; Kachroo et al. 2005) and cannabinoid CB_1 receptors (Lerner et al. 2010; Ferre et al. 2010). $A_{2A}Rs$ are also present at corticostriatal projections, mostly located at synapses (Rosin et al. 2003; Rebola et al. 2005a), where they modulate glutamate release that drives striatal neurons (Rebola et al. 2005a; Ciruela et al. 2006). Accordingly, striatal $A_{2A}R$ activation has been documented to promote LTP at the cortico-accumbal synapses (D'Alcantara et al. 2001) and spike-timing-dependent LTP at glutamatergic synapses onto the striatopallidal neurons (Shen et al. 2008a, b) and LTP at the cortico-striatopallidal synapses with FGFR co-activation (Flajolet et al. 2008). Thus $A_{2A}Rs$ at the corticostriatal pathway modulate synaptic plasticity underlying cognition by uniquely integrating dopamine and glutamate signaling in the striatum.

$A_{2A}R$-dopamine interaction: This $A_{2A}R$ facilitation of LTP process by a kinase A (PKA)-dependent mechanism of Ca^{2+} entry through NMDA receptors at the corticostriatal terminal counters the D_2R-mediated inhibitory effect on this synapse (Higley and Sabatini 2010). The intracellular cAMP levels in the striatopallidal neurons dictate bidirectional synaptic plasticity in the striatopallidal neurons in response to the corticostriatal afferent activity (Ferre et al. 2010). Through Gs-coupled $A_{2A}R$ (Mori and Shindou 2003) and Gi-coupled D_2R bidirectional regulation of cAMP signaling, concurrent activation of $A_{2A}Rs$ and D_2Rs in the striatopallidal neurons allow the integration of cAMP signaling and modification of synaptic plasticity in the striatopallidal neurons for behavioral adaptation. The postsynaptic striatal $A_{2A}R$ activation converts striatal LTD, the predominant form of long-term plasticity in the striatum, into LTP by countering D_2R effect (Ferre et al. 1997; Ongini and Fredholm 1996). Because phasic dopamine neuron firing

acts as a "prediction error" signal that causes learning (Kachroo et al. 2005; Lerner et al. 2010), striatopallidal A_{2A}Rs can modify dopamine signal to influence learning and memory through the A_{2A}R-D_2R interaction.

A_{2A}R-glutamate interaction: Glutamate (sensorimotor) signal at the corticostriatal pathway is crucial to striatal synaptic plasticity (such as spike time-dependent plasticity, STDP (Sebastiao and Ribeiro 2000) and the "gain" control of cortical incoming information. A_{2A}Rs may regulate glutamate signaling through its presynaptic control of glutamate release and postsynaptic interaction with NMDA receptors and mGluR5. The A_{2A}R is postulated to selectively engage in the implementation of synaptic changes in this excitatory synapses (Cunha 2008b). This facilitating role of A_{2A}R activation is accomplished by increasing glutamate release (Rodrigues et al. 2005), by facilitating NMDA receptor-mediated responses (Rebola et al. 2008) and by desensitizing presynaptic inhibition of A_1R (Lopes et al. 2002; Ciruela et al. 2006) or cannabinoid CB_1R (Martire et al. 2011).

By those distinct mechanisms, A_{2A}Rs at the corticostriatal pathway are critically important for the integration of incoming information (glutamate sensorimotor signal) and neuronal sensitivity to this incoming information (dopamine reinforcement signal) to control Hebbian synaptic plasticity, learning, and memory (Cunha 2008a, b; Schiffmann et al. 2007; Chen 2014).

Hippocampal A_{2A}Rs are localized postsynaptically at synapses between mossy fibers and CA3 pyramidal cells, and activation of hippocampal A_{2A}Rs modulates synaptic plasticity through multiple mechanisms, involving a postsynaptic NMDA-dependent LTP induced by short bursts of mossy fiber stimulation (Rebola et al. 2008), or AMPA-evoked LTP at the CA3-CA1 synapse by a PKA-dependent GluR1 phosphorylation at the Ser845 (Dias et al. 2012), or the kainate receptor-mediated LTD (*KAR LTD*) induced by high-frequency mossy fiber stimulation, natural spike patterns (Chamberlain et al. 2013), and BDNF-mediated LTP (Fontinha et al. 2008). In a trace eyeblink conditioning paradigm, A_{2A}R blockade inhibits experimentally evoked LTP at the CA3-CA1 synapses in the hippocampus and conditioned response behaviors (Fontinha et al. 2009). In another eyeblink conditioning paradigm from the turtle, in which the cranial nerves are directly stimulated in place of using a tone or air puff, phosphorylated 3-phosphoinositide-dependent kinase-1 (p-PDK1) has been found to increase and decrease, respectively, to paired and unpaired nerve stimulation, with the opposing actions of neurotrophin receptors TrkB and p75 (NTR). Both of these effects are blocked by the A_{2A}R antagonist. It is attributed to unique actions of A_{2A}R to activate Gs signaling and to transactivate TrkB for convergent activation of PDK1 and protein kinase A to initiate classical conditioning during paired stimulation.

15.4 The Tools for Studying Adenosine Receptor Control of Cognition in Behaving Animals

Various pharmacological, genetic, and optogenetic approaches have been used to provide a comprehensive assessment of the impact of each AR subtype in distinct brain regions (e.g., hippocampus, cortex, striatum) on various information processes

(e.g., encoding, storage, consolidation, retrieval) using different behavioral tasks. Earlier studies on the AR control of cognition mostly exploited AR antagonists and agonists to reveal the role of adenosine and its receptor targets in learning and memory. However, these pharmacological studies are limited by their partial specificity of AR drugs. Coupling pharmacological studies with complementary AR knockouts (KO) can overcome this limitation to provide some clarifications of the impact of $A_{2A}R$ and A_1R signaling on various tasks of learning and memory. These global genetic KO studies may, however, be confounded with potential developmental effects. Importantly, using pharmacological tools or even a global AR KO strategy, it is difficult to dissect out the specific contributions of the different AR subtypes in distinct brain regions. To address this issue, conditional KO of $A_{2A}R$ and A_1R genes in defined brain regions (e.g., cerebral cortex versus striatum versus hippocampus) and cell types (e.g., neurons versus astrocytes) has been achieved using the Cre-loxP system (for review see Wei et al. 2011a). Region-specific deletion of $A_{2A}Rs$ has been achieved in the forebrain (i.e., striatum, cerebral cortex, hippocampus) (Bastia et al. 2005; Yu et al. 2008), striatum (Shen et al. 2008a, b), and astrocytes (Matos et al. 2015). In addition, development of adeno-associated virus (AAV) vector carrying short-hairpin RNA targeted to produce site-specific silencing of the $A_{2A}R$ gene (Lazarus et al. 2011; Simoes et al. 2016) and local injection of AAV vectors containing the *cre* transgene into the brains of mice carrying loxP-flanked A_1R or $A_{2A}R$ genes (Scammell et al. 2003; Lazarus et al. 2011) have been used to achieve a temporal and regional specificity. This allow us to the previously uncover underappreciated functions of adenosine receptors in these brain regions, including focal knockdown of the A_1R in hippocampal CA1 or CA3 neurons (Scammell et al. 2003) and $A_{2A}Rs$ in the nucleus accumbens (Lazarus et al. 2011), dorsomedial striatum (Li et al. 2018), dorsolateral striatum (Li et al. 2016), hippocampus (Wei et al. 2014), and amygdala (Simoes et al. 2016). Finally, recent development of optogenetics by light control of neuronal activity with genetically engineered optical proteins (e.g., channelrhodopsin-2 and Arch) (Boyden et al. 2005; Deisseroth 2014; Yizhar et al. 2011) or chemicogenetic control of G-protein signaling by the directed molecular evolution of designer receptors exclusively activated by designer drugs (DREADD) (Farrell et al. 2013; Giguere et al. 2014) has potentiated dissection of specific brain circuits underlying cognition. To study cognitive behaviors such as working memory at the time scale of seconds, we have developed the novel opto-$A_{2A}R$ method to optogenetically control $A_{2A}R$ signaling in defined brain circuits of behaving animals, which enables us to interrogate the causal involvement of $A_{2A}R$ signaling in cognition with unparalleled spatiotemporal resolution (Li et al. 2015a, 2018).

15.5 Adenosine Receptor Modulates Learning and Memory in Normal Animals

Over the last two decades, neurochemical, pharmacological, and genetic knockout studies coupled with diverse sets of behavioral paradigms have begun to reveal the complexities and vastness of AR functions in cognition. Consistent with the ability

of the $A_{2A}R$ to integrate dopamine and glutamate signaling and to modulate synaptic plasticity (LTP in the hippocampus and LTP/LTD in the striatum) (D'Alcantara et al. 2001; Rebola et al. 2008), increasing evidence supports that brain $A_{2A}R$ activity contributes to modulation of learning and memory (Cunha et al. 2008; Cunha 2008b; Shen et al. 2008a, b; Ferre et al. 2008). Under physiological conditions, the $A_{2A}R$ exerts control over a variety of cognitive behaviors: (i) *short-term recognition memory*, as assessed using olfactory discrimination and social recognition memory (Prediger et al. 2005a, b; Prediger and Takahashi 2005), spatial recognition memory, and novelty exploration in Y-maze testing (Wang et al. 2006); (ii) *spatial working memory* (SWM) by radial maze tests (Gimenez-Llort et al. 2007) repeated trials of the Morris water maze and T-maze-based delay-non-match-to-place test (Li et al. 2018; Zhou et al. 2009); (iii) *reversal learning* as assessed by spatial reversal learning paradigm (Wei et al. 2011b); (iv) *goal-directed* vs *habitual behaviors* by satiety-based instrumental paradigm (Li et al. 2016; Hikida et al. 2013); (v) *Pavlovian fear conditioning* by eyeblink conditioning and context and tone fear conditioning (Wei et al. 2014; Hikida et al. 2013); (vi) *aversive learning* by conditioned taste aversion, avoidance behavior using an aversive paradigm, a one-trial inhibitory avoidance task (Pereira et al. 2005; Singer et al. 2013; Kopf et al. 1999); (vii) *effort-related decision-making and effort expenditure* (O'Neill and Brown 2007; Pardo et al. 2012; Pereira et al. 2011; Mott et al. 2009; Mingote et al. 2008); and (viii) *conditional temporal probability* by a task to dissociate the effect of elapsing time in the foreperiod and conditional temporal probability of the imperative stimulus (O'Neill and Brown 2007). Recent studies with refined conditional cell-specific $A_{2A}R$ KO, AAV-based shRNAi interference, and especially optogenetic control of $A_{2A}R$ signaling with unparalleled spatiotemporal resolution have offered several new insights into $A_{2A}R$ ability to fine-tune cognition under physiological conditions. Dissecting the impact of the $A_{2A}R$ on some forms of learning and memory is now leading to the new insights and better understanding of the mechanism underlying the $A_{2A}R$ control of cognition.

15.5.1 Striatopallidal A_{2A} Receptors Function as a Common "Break" Mechanism to Constrain Learning and Memory

Over the last several years, genetic KO studies have shown that the genetic deletion of $A_{2A}R$ or CD73 improves SWM, as gauged from the analysis of repeated acquisition paradigm in the Morris water maze or the 8-arm radial maze (Wei et al. 2011a; Zhou et al. 2009). Moreover, an improved WM is achieved by genetic deletion of $A_{2A}R$ either globally (i.e., global-$A_{2A}R$-KO) or by a selective deletion in the entire forebrain neuron (i.e., cerebral cortex, hippocampus, and striatum; fb-$A_{2A}R$-KO). Genetic deletion of $A_{2A}R$ selectively in the striatal neurons (st-$A_{2A}R$-KO) is sufficient to bolster SWM (Wei et al. 2011a; Zhou et al. 2009), Pavlovian fear conditioning (Wei et al. 2014), reversal learning (Wei et al. 2011b), and goal-directed behavior (Yu et al. 2009). Furthermore, bidirectional manipulations of the striato-

pallidal A_{2A}Rs by optogenetic activation of A_{2A}R signaling and Cre-mediated knockdown of A_{2A}Rs in the DMS unambiguously demonstrated that A_{2A}Rs in the DMS exert an inhibitory control of goal-directed behavior (Li et al. 2016). These findings are consistent with the fact that pharmacological reduction of A_{2A}R-mediated PKA-pCREB signaling in the DMS enhances acquisition of goal-directed ethanol drinking behaviors (Nam et al. 2013) and that A_{2A}R antagonists counter the D_2R antagonist effect and enhance effort-related decision-making in several behavioral paradigms including T-maze cost/benefit procedure and choosing voluntary exercise over sucrose consumption (Pardo et al. 2012; Pereira et al. 2011; Mott et al. 2009; Mingote et al. 2008; Correa et al. 2016). Notably, a recent study has demonstrated that A_{2A}R antagonism promoted impulsive responses during Pavlovian conditioning and the 5-choice serial reaction time task (5-CSRTT), with the reduced ERK1 and ERK2 phosphorylation in the dorsal hippocampus (dHip) (Oliveros et al. 2017). Collectively, these findings from diverse learning paradigms led us to propose that striatopallidal A_{2A}Rs function as a common "break" mechanism to constrain cognition (Chen 2014).

Although the striato-cortical interaction is mostly conceived as supporting the control of actions and procedural memory, there is an increasing recognition that striatal circuits are also actively involved in the control of declarative and episodic memory (Wei et al. 2011a, b; Simpson et al. 2010; Kellendonk et al. 2006; Li et al. 2011; Ito et al. 2008; Ferretti et al. 2010). In fact, the connectivity between the ventral striatum and the hippocampus (van Groen and Wyss 1990; Matthews et al. 2004; MacAskill et al. 2012) is involved in the retrieval of cue contingencies based on spatial locations and in the control of spatial behavior (Ito et al. 2008; Ferretti et al. 2010; Seamans and Phillips 1994; Maldonado-Irizarry and Kelley 1995; Floresco et al. 1997; Gengler et al. 2005; McDonald et al. 2006). With the increasing acceptance that the ventral striatum acts as an integrative unit associated with the adaptive encoding of working memory (Simpson et al. 2010; Scimeca and Badre 2012; Hallock et al. 2013) and reinforcement learning (Johnson et al. 2007; Piray 2011; Pennartz et al. 2011; van der Meer and Redish 2011; Liljeholm and O'Doherty 2012), it is possible to propose the striatopallidal pathway in the ventral striatum as a global inhibitory control system for declarative and episodic memory: this concept is based on the emerging evidence that the activity of the striatopallidal pathway provides inhibitory control for novel object recognition test (Durieux et al. 2012), amphetamine sensitization (Bateup et al. 2010), instrumental learning (Yu et al. 2009; Lobo et al. 2007), addiction (Durieux et al. 2009; Lobo et al. 2010), and probably goal-oriented behavior (Yu et al. 2009) and biases during decision-making (Tai et al. 2012). In this context, the proposed "a common break mechanism" by striatopallidal A_{2A}R activation provides a framework for a pharmacological strategy to improve cognitive deficits in aging and neuropsychiatric disorders by blocking striatopallidal A_{2A}R activity.

Notably, shA_{2A}R-mediated focal knockdown of the A_{2A}R in the brain regions outside the striatum, including the basolateral complex of the amygdala (Simoes et al. 2016), the ventral hippocampus (Wei et al. 2014), and the prefrontal cortex (Li et al. 2016), produced a facilitating effect of the A_{2A}R on Pavlovian fear

conditioning (Simoes et al. 2016; Wei et al. 2014) and SWM (Li et al. 2018). Together, these findings showed the brain-region-specific modulation of cognition by the $A_{2A}R$ activity.

15.5.2 Temporally Precise Integration of $A_{2A}R$ Signaling with Dopamine and Glutamate Signaling on the Striatopallidal Neurons for Cognitive Behavioral Control

The contemporary reinforcement learning theory postulates the "three-factor rule" of striatal plasticity underlying striatum-dependent learning: synaptic strength is regulated by spatiotemporally precise integration of nigra-striatal dopamine signal (the reinforcement signaling from the environment) and corticostriatal glutamate signaling (value coding from the reward history) to converge on the striatopallidal neurons for coding of the action and outcome/reward relationship (Yagishita et al. 2014; Augustin et al. 2014; Aquili et al. 2014). Consistent with this view, neurons in the prefrontal cortex fired selectively to rewarded (but not unrewarded) lever presses and precisely at the time of the reward delivery (Burgos-Robles et al. 2013). Furthermore, time-locked optogenetic stimulation of nigral dopamine and cortical glutamate (within 0.3–2 s) is critical to the modulation of striatal synaptic plasticity (Yagishita et al. 2014). The significance of the temporal relationship of dopamine, glutamate, and striatal signaling is demonstrated by optogenetic control of behaviors (such as stimulus-reward contingency) with the concurrent optogenetic stimulation of the striatal neurons with the onset of cue (within 5 ms but not 150 ms) (Tai et al. 2012) and by optogenetic inhibition of ventral striatal neurons in the time segment (1.5 s) between action selection and outcome (but not other time segments) (Aquili et al. 2014). According to this working hypothesis, concurrent activation of dopamine signal triggered by a motivationally significant event such as reward delivery with a postsynaptic striatal signal such as striatopallidal $A_{2A}R$ activity is critical to the striatum-dependent reinforcement learning (Schultz et al. 1997; Reynolds et al. 2001). Striatopallidal $A_{2A}Rs$ may modulate instrumental learning by acting precisely at the time of the reward to interact with the reward-triggered dopamine and glutamate signaling. Alternatively, striatopallidal $A_{2A}Rs$ may control instrumental learning, by modulating the vigor of actions without affecting the animal's action decision (Desmurget and Turner 2010), by modulating the "off-line" processing of incoming signaling (glutamate) for instrumental behavior (Pomata et al. 2008), or by providing a permissive role in learning association (Brainard and Doupe 2000). In these schemes of the vigor of action, "off-line" coding, or permissive effect, the temporal relationship between the $A_{2A}R$ activity and the reward is not essential. Due to the lack of methods to control $A_{2A}R$ signaling in freely behaving animals with required spatiotemporal resolution, the temporal relationship between $A_{2A}R$ signal and the reward-triggered dopamine and glutamate signaling in the control of instrumental behaviors was unknown until recently. Using our "opto-$A_{2A}R$"

method to optogenetically control the $A_{2A}R$ signaling at the millisecond resolution (Li et al. 2015a), we demonstrated that "time-locked" (but not "random") optogenetic activation of the striatopallidal $A_{2A}R$ signaling at the time of the reward is sufficient to affect instrumental behavioral modes (Li et al. 2015a). These studies define the effective temporal window whereby the striatopallidal neuronal activity (and striatopallidal $A_{2A}R$ activity) modulates learning and memory in the close temporal relationship with dopamine and glutamate signaling associated with cue and reward (Schultz et al. 1997; Reynolds et al. 2001). This integration may affect the intracellular cAMP level by concurrent activation of the D_2 receptor, NMDA receptors, and $A_{2A}R$ in the striatopallidal neurons, dictating bidirectional synaptic plasticity in the striatopallidal neurons for coding of the mode of instrumental learning behavior (Augustin et al. 2014). Interestingly, in the CA1 region of the hippocampus, enhanced NMDAR-dependent neuronal excitability by co-activation of mGluR5 and NMDARs is permitted by the $A_{2A}R$ activation, temporally coinciding with the robust increase in Src kinase-dependent NR2B (Tyr1472) phosphorylation (Sarantis et al. 2015). These studies provide new molecular insights into the temporal integration of adenosine-glutamate signaling in the hippocampus.

15.5.3 Dissecting AR Control of Distinct Information Processing Phases

Cognitive control of SWM involves multiple executive processes including encoding, maintenance, and retrieval of information, but the AR modulation of these SWM processes remains undefined due to lack of the methods to control AR signaling with the temporal resolution of seconds. The recent development of optogenetic control of $A_{2A}R$ signaling has provided a unique opportunity to address this issue. The specificity of opto-$A_{2A}R$ signaling (Li et al. 2015a) and the temporal resolution of the opto-$A_{2A}R$ are validated by the rapid electrophysiological response (within 3–18 s) (Li et al. 2018) and biochemical detection of opto-$A_{2A}R$-induced cAMP accumulation within 30 s (Li et al. 2015a) after opto-$A_{2A}R$ activation by light, which is consistent with the temporal resolution (within seconds) of opto-dopamine D1 receptor and opto-adrenergic α1 and ß2 receptors (Airan et al. 2009; Gunaydin et al. 2014). The opto-$A_{2A}R$ approach allowed us to demonstrate that optogenetic activation of striatopallidal $A_{2A}R$ signaling selectively during *the delay or retrieval* (but not *encoding*) phase impairs SWM performance (Li et al. 2018). Similarly, opto-$A_{2A}R$ activation in mPFC precisely during the *delay* phase (but not the *encoding and retrieval* phase) affects SWM performance (Li et al. 2018). This suggests that the cortico-striatopallidal $A_{2A}R$ signaling is critical to the *maintenance* (striatal and mPFC $A_{2A}Rs$) and *retrieval* (striatal $A_{2A}Rs$) processes of SWM. Lack of the effect of the striatopallidal $A_{2A}R$ activity on the coding of sensory information of SWM is apparently consistent with the previous finding that genetic KO or optogenetic activation of striatopallidal $A_{2A}R$ activity did not affect the acquisition or omission/extinction phases of instrumental learning (Yu et al. 2009; Li et al. 2016). These

findings of the distinct modulation of the three phases of SWM (i.e. encoding, maintenance, and retrieval) by optogenetic $A_{2A}R$ signaling in mPFC and striatum complement the recent ChR2-based optogenetic studies uncovering the vHPC-mPFC projections in the encoding of SWM (Spellman et al. 2015), the mPFC in the maintenance (Liu et al. 2014), and the medial entorhinal cortex (MEC)-hippocampal-thalamus nucleus circuit in the retrieval of SWM (Yamamoto et al. 2014). Collectively, these findings provide the potential circuit framework for passaging SWM information flow from the encoding (vHPC→mPFC projection) to the maintenance (mPFC, striatum, and thalamus) to the retrieval (MEC → HPC → ST → TH loop).

15.5.4 A_1 Receptors and Learning and Memory

For its wide and abundant expression patterns in various brain regions associated with learning and memory, and for its profound effect on neurotransmission, A_1Rs are traditionally thought to execute adenosine's potential modulatory effects on cognition. In line with the evidence of the A_1R control of mainly "basal" synaptic transmission, earlier pharmacological studies support the role of the A_1R control of learning and memory. For example, hippocampal A_1Rs influence working memory (Ohno and Watanabe 1996), prevent scopolamine-induced working memory deficits (Hooper et al. 1996), and prevent morphine-induced impairment in the retrieval of a spatial reference memory (Lu et al. 2010). However, studies from A_1R-KO mice suggest that A_1Rs may not be critical to some mnemonic effects of adenosine because A_1R-KO mice showed normal performance in the water maze, normal acquisition and retention of a spatial reference memory, normal SWM performance, and normal ability to learn the new position of a fixed platform during reversal learning in two different A1R-KO mouse lines (Gimenez-Llort et al. 2002, 2005; Lang et al. 2003). Thus, under physiologic conditions, the A_1R may not be crucial for the expression of normal spatial reference memory or SWM. It should be noted that an altered emotional status (Gimenez-Llort et al. 2002; Johansson et al. 2001) and a possible confounding developmental effect of A_1R KO in mice on A_1R control of cognition cannot be ruled out.

15.6 A_{2A} Receptor Antagonism Reverses Memory Impairments Under Various Pathological Conditions

Cognitive impairment is prevalent on aging and is accelerated in a pathognomonic manner in such neurodegenerative disorders as Alzheimer's disease (AD) and Parkinson's disease (PD), with the greatest socioeconomic impact in the Western world (Murray and Lopez 1997; Olesen et al. 2012; Wimo et al. 2013). Currently, there is no disease-modifying treatment to slow down or hold the disease progression.

The early symptoms associated with mild cognitive impairment (MCI), often evolving to AD (Landau et al. 2010; Ewers et al. 2012; Weintraub et al. 2012), are the emergence of short-term memory (STM) impairments with working memory (WM) deficit at its core (Baddeley et al. 1991; Baddeley 2003; Albert 1996; Grady et al. 2001; Belleville et al. 2008; Sperling et al. 2010; Koppel et al. 2014). Since 1993, FDA has approved three acetylcholinesterase inhibitors and an NMDA receptor antagonist memantine for improving cognition at early-moderate (AChE inhibitors) and moderate-later stage (memantine) of the AD (Aisen et al. 2012). However, these treatments do not have disease-modifying properties, and their use is limited by the poor efficacy (only 25% patients responded to the treatment) (Aisen et al. 2012; Amanzio et al. 2012; Jones 2010; Chaudhuri and Schapira 2009). The use of cholinesterase inhibitors to manage early cognitive impairments in PD patients may worsen their motor deficits (Chaudhuri and Schapira 2009; Richard et al. 2002; van Laar et al. 2011). Thus, identification and intervention at the earliest stage of AD/PD-MCI is a crucial unmet need for the overall care of AD/PD patients. In this context, experimental evidence suggests that pathological brain conditions associated with memory impairment (such as AD, stress, and inflammation) are accompanied by a local increase of the extracellular levels of adenosine (Cunha et al. 2001) and an upregulation and aberrant signaling of the brain $A_{2A}R$ (Chen et al. 2013; Cunha and Agostinho 2010). This led to the demonstration that blocking the "abnormal" activation of $A_{2A}R$ in specific brain regions (e.g., the hippocampus) confers protection against memory impairments under pathological conditions. Accordingly, under various pathological conditions, $A_{2A}R$ blockade prevents or reverses memory impairments caused by Aβ peptides via p38 MAPK pathway (Canas et al. 2009a; Dall'igna et al. 2007) and in transgenic hAPP AD model (Orr et al. 2015), in R6/2 transgenic model of HD (Li et al. 2015b), in the PD model with focal dopamine depletion in the cortex (Kadowaki Horita et al. 2013) or local injection of A53T α-Syn fibrils (Hu et al. 2016), and in the controlled cortical impact model and blast-induced traumatic brain injury (Ning et al. 2013; Zhao et al. 2017a, b) or caused by acute cannabinoid CB1 receptor activation (Mouro et al. 2017) and sporadic dementia (Espinosa et al. 2013). The involvement of the $A_{2A}R$ in pathological cognitive impairment is further supported by targeted neurogenesis gene-based association analysis in cognitively normal and impaired participants, leading to identification of $A_{2A}R$ gene (ADORA2A) as significantly associated with hippocampal volume (Horgusluoglu-Moloch et al. 2017).

15.6.1 The Aberrantly Increased $A_{2A}R$ Signaling in Cognition-Relevant Regions Is Sufficient to Trigger Memory Impairment

Under pathologic conditions, such as trauma and seizure, the activation of postsynaptic neurons can lead to the adenosine release, contributing to adenosine-mediated synaptic depression, an autonomic feedback mechanism to suppress excitatory

transmission during prolonged activity (Lovatt et al. 2012; Klyuch et al. 2012). Noxious brain conditions enhance the extracellular levels of ATP and the extracellular conversion of AMP into adenosine via CD73 enzyme (Zimmermann 2000). Furthermore, the density of hippocampal A_{2A}Rs, localized abundantly in hippocampal synapses (Rebola et al. 2005a), in particular in glutamatergic synapses (Rebola et al. 2005a), increases in aged animals (Canas et al. 2009b; Cunha et al. 1995; Lopes et al. 1999b; Rebola et al. 2003) and human AD (Albasanz et al. 2008), in transgenic mice displaying memory impairments (Espinosa et al. 2013; Cunha et al. 2006; Cognato et al. 2010), in the frontal cortex (mainly A_{2A}Rs in astrocytes) of AD brains (Orr et al. 2015), in the putamen of early (Braak PD stage 1–2) stage of PD (Villar-Menendez et al. 2014), and in the caudate of dyskinetic PD brains (Ramlackhansingh et al. 2011; Mishina et al. 2011). Interestingly, a recent study shows that the upregulation of astrocytic A_{2A}R in the hippocampus and neocortex of aging mice is induced by elevated levels of Aβ, C-terminal fragments of the amyloid precursor protein (APP), or amyloid plaques, but not overexpression of APP per se (Orr et al. 2018). This view of aberrantly increased A_{2A}R signaling is supported by the striking induction of the A_{2A}R in the hippocampus after A53T α-Syn fibril injection (Hu et al. 2016). Thus, the upregulated A_{2A}Rs may serve as a biomarker for PD and AD. Because several positron emission tomography (PET) ligands for the A_{2A}R, such as the A_{2A}R antagonist ligand [^{11}C]-SCH442416 and [^{11}C]-KW6002, have been developed and successfully employed to measure the level of striatal A_{2A}Rs of PD patients (Ramlackhansingh et al. 2011; Mishina et al. 2011; Khanapur et al. 2014), it would be essential to investigate whether these A_{2A}R antagonistic PET ligands can be used as an early diagnostic biomarker for AD and PD.

Is the aberrantly increased adenosine-A_{2A}R signaling a maladaptive consequence of aging, PD and AD pathologies, or a causal factor in the emergence of memory deficits? The finding that light activation of opto-A_{2A}R signaling in hippocampal neurons is sufficient (in the absence of neurodegeneration) to trigger memory impairment (Li et al. 2015a) argues that the marked upregulation of A_{2A}R expression in the hippocampus may be responsible (at least partially) for the development of A53T α-Syn-induced cognitive impairments. Similarly, the activation of A_{2A}Rs with CGS 21680 before the training session is also sufficient to trigger memory impairment in the object recognition task, inhibitory avoidance, and modified Y-maze in naive mice (Pagnussat et al. 2015). Transgenic overexpression of the A_{2A}R in the cortex amplified the synaptic plasticity and memory deficits triggered by GR in the hippocampus, which was reversed by A_{2A}R antagonism (Batalha et al. 2016). This is in line with the "common break" mechanism by activation of the striatopallidal A_{2A}Rs to constrain a variety of cognitive behaviors under physiological conditions (Li et al. 2016). This insight is validated by the reversal of A53T α-Syn fibril-induced working memory deficit by genetic deletion of A_{2A}Rs. In agreement with this view, A_{2A}R blockade can prevent memory dysfunction caused by Aβ peptides via p38 MAPK pathway (Canas et al. 2009a; Dall'igna et al. 2007) and in transgenic hAPP AD model (Orr et al. 2015, 2018) and R6/2 transgenic model of HD (by A2AR antagonists alone or in combination with D1R antagonists) (Li et al. 2015a, b; Tyebji et al. 2015), by the PD model with focal

dopamine depletion in the cortex (Kadowaki Horita et al. 2013), by controlled cortical impact model of traumatic brain injury (Ning et al. 2013, Zhao et al. 2017a, b), by chronic unpredictable stress (Kaster et al. 2015), and by sporadic dementia (Espinosa et al. 2013). Demonstration of the hippocampal $A_{2A}R$ upregulation by A53T α-Syn fibrils and the reversal of α-Syn-induced cognitive impairments, together with the demonstration of the sufficiency of optogenetic activation of $A_{2A}R$ signaling to induce cognitive impairments (Li et al. 2015a), suggest a plausible mechanism linking α-Syn to cognitive impairments in the absence of neurodegeneration. In the stress model induced by maternal separation, the $A_{2A}R$ blockade effectively reverted the behavior and electrophysiological and morphological impairments, with the restoration of the hypothalamic-pituitary-adrenal axis (HPA-axis) activity (Batalha et al. 2016).

On the other hand, the role of astrocytic $A_{2A}Rs$ in the development of cognitive impairment is not clear: selective deletion of astrocytic $A_{2A}Rs$ exhibited enhanced MK-801 psychomotor response and decreased working memory, accompanied by a disruption of glutamate homeostasis characterized by increased GLT-I activity and internalization of AMPA-R (Matos et al. 2015). In a mouse hAPP model of AD, chemogenetic activation of astrocytic Gs-coupled signaling (mimicking upregulation of astrocytic $A_{2A}Rs$ in human AD cortex) impaired long-term memory, while conditional genetic removal of these receptors enhanced memory (Orr et al. 2015). This justifies a need for additional studies to clarify the exact role of astrocytic ARs in cognitive control under normal and pathological conditions.

15.6.2 $A_{2A}R$ Inactivation Reverses Cognitive Impairments in Neurodegenerative Disorders by Modifying Aggregate Protein Processing and Countering Synaptopathy

MCI and early AD and PD are often associated with the changes in the brain levels of different forms of β-amyloid peptides, amyloid plaques, neurofibrillary tangles with phosphorylated Tau proteins for AD (Galasko et al. 1998; Andreasen et al. 2001; Riemenschneider et al. 2002; Mattsson et al. 2009), and α-synuclein aggregates for PD (Brundin and Melki 2017; Goedert et al. 2017; Masuda-Suzukake et al. 2013), argued to be major culprits of AD and PD (Hardy and Selkoe 2002; Walsh and Selkoe 2004). Increasing evidence points to the novel mechanism that $A_{2A}R$ inactivation protects against pathological cognitive impairments by modification of proteins that trigger neurodegeneration, including β-amyloid synaptopathy (Canas et al. 2009a; Cao et al. 2009), α-synuclein (Laurent et al. 2016; Ferreira et al. 2017), and Tau protein (Laurent et al. 2016). (I) Studies of aged AD transgenic (APPsw, Swedish mutation) mice found that caffeine (nonselective adenosine antagonist) treatment (1.5 mg daily dose, equivalent to 500 mg in human) to APPsw mice reduced brain Aβ levels with reduced presenilin 1 (PS1) and beta-secretase (BACE) expression, leading to protection against certain cognitive

impairments (Cao et al. 2009; Arendash et al. 2006, 2009). (II) Three recent studies (including ours) strongly support the $A_{2A}R$ modulation of α-synuclein aggregation by showing decreased α-Syn aggregation in the hippocampal neuron with reduced number of pSer129 α-Syn-rich and p62-positive inclusions in $A_{2A}R$-KO mice (Hu et al. 2016), decreased the percentage of cells displaying α-Syn inclusions in cultured cells after $A_{2A}R$ antagonist treatment (Ferreira et al. 2017), and attenuated toxicity of α-Syn aggregates in vitro and in a yeast proteotoxicity model of PD after caffeine treatment (Kardani and Roy 2015). These findings are in line with the previous study showing that the $A_{2A}R$ KO prevents loss of dopaminergic neurons caused by the transgenic overexpression of intracellular human α-Syn containing both A53T and A30P mutations (Kachroo and Schwarzschild 2012). (III) In a THY-Tau22 model of AD, genetic deletion of the $A_{2A}R$ protects from Tau pathology-induced deficits in terms of spatial memory and hippocampal long-term depression, with a concomitant decrease in Tau hyperphosphorylation, normalization of the hippocampal glutamate/GABA ratio, and a global reduction in neuroinflammatory markers (Laurent et al. 2016). The $A_{2A}R$ antagonist MSX-3 also improved memory and reduced Tau hyperphosphorylation in THY-Tau22 mice (Laurent et al. 2016). In the controlled cortical impact model of traumatic brain injury (TBI), genetic deletion of the $A_{2A}R$ or treatment with the $A_{2A}R$ antagonist ZM241385 or caffeine reduced the level of Tau phosphorylation at Ser404 and alleviated spatial memory dysfunction (Zhao et al. 2017b). Interestingly, 14-month-old proaggregant-Tau-transgenic mice developed neuronal and astrocytic hypoactivity and presynaptic dysfunction, which were reversed by treatment with A_1R rolofylline (KW-3902) (Dennissen et al. 2016). (IV) On the other hand, in HD model, $A_{2A}R$ activation enhanced proteasome activity and reduced mutant huntingtin aggregations through the PKA-dependent pathway (Huang et al. 2011; Chiang et al. 2009). Collectively, these findings support that AR antagonists including caffeine may attenuate PD and PD pathology by a mechanism other than proteasome pathway.

Furthermore, MCI and early AD and PD are also associated with the loss of synapses in defined brain cortical regions, most evident in the hippocampus in MCI and early phases of AD (Scheff et al. 2007; Coleman et al. 2004; Selkoe 2002) and during aging (Burke and Barnes 2010; Morrison and Baxter 2012). In fact, a synapse is the primary target of toxic Aβ oligomers (Hardy and Selkoe 2002), and the loss of synapses in the hippocampus is probably the earliest morphological trait and the best correlated with initial memory impairment in AD (Coleman et al. 2004). Indeed, $A_{2A}R$s are most abundant in hippocampal synapses (Rebola et al. 2005b), in particular in glutamatergic synapses (Rebola et al. 2005b). The density of hippocampal $A_{2A}R$ increases in aged animals (Canas et al. 2009b; Cunha et al. 1995; Lopes et al. 1999b; Rebola et al. 2003) and human AD (Albasanz et al. 2008) as well as in transgenic mice displaying memory impairments (Espinosa et al. 2013; Cunha et al. 2006; Cognato et al. 2010). In AD model with the intracerebral administration of soluble Aβ(1–42) (2 nmol) in rats or mice, memory impairment and a loss of nerve terminal markers without overt neuronal loss, astrogliosis, or microgliosis were observed, whereas the $A_{2A}R$ antagonist SCH58261 (50 nm) prevented

the initial synaptotoxicity (loss of MAP-2, synaptophysin, and SNAP-25 immunoreactivity), through the p38-dependent and cAMP/PKA-independent pathways (Canas et al. 2009a). Similarly, pharmacological and genetic blockade of $A_{2A}R$ and caffeine treatment efficiently prevented chronic unpredictable stress-induced memory deficits and the associated loss of synapses, typified by a decrease in synaptic plasticity and a reduced density of synaptic proteins (synaptosomal-associated protein 25, syntaxin, and vesicular glutamate transporter type 1) (Kaster et al. 2015). Altogether, these evidences indicate that the $A_{2A}R$ plays an effective role in modifying aggregated protein processing and counteracting synaptopathy, both of which contribute to memory function preservation.

15.6.3 $A_{2A}R$ Antagonist Control of Cognition in Nonhuman Primates

Higher cognitive disorders in humans involve the association cortex, which is regulated in a fundamentally different manner from the older sensory-motor cortical and subcortical circuits and thus is not suitable to study in rodent models, whose brains have a very small association cortex (Goldman-Rakic 1987). For the complex nature of higher cognition functions in human, developing the effective pharmacological strategy to improve cognition would require preclinical data from nonhuman primates because higher cognitive functions involve the association cortices, which are evolutionally poorly developed in rodents and thus cannot be adequately addressed by standard pharmacological and genetic studies in rodent models (Goldman-Rakic 1987). In recent clinical trials of $A_{2A}R$ antagonists and caffeine for motor benefits in PD, the possible cognitive effects of $A_{2A}R$ antagonists and caffeine were not evaluated (Aarsland et al. 2010), in part due to the lack of cognitive behavior data from nonhuman primate model of PD. Besides increasing evidence from rodent models of PD supporting that pharmacological and genetic inactivation of $A_{2A}Rs$ can prevent WM dysfunction under multiple pathological conditions (for a review see Chen 2014), two studies have addressed this knowledge gap by testing $A_{2A}R$ antagonists (such as istradefylline in a clinical trial) in nonhuman primate models of PD (Li et al. 2018). In the MPTP-treated macaque model of parkinsonian and dyskinetic motor symptoms, the $A_{2A}R$ antagonist istradefylline reduced the attentional and working memory deficits caused by l-DOPA (Ko et al. 2016). In MPTP-treated cynomolgus monkeys coupled with delay-non-match-to-sample/place (DMTS/DMTP) paradigm, we showed that the $A_{2A}R$ antagonist KW6002 ameliorated spatial working memory deficits (Li et al. 2018). Identification of the proper dose and the treatment paradigm of the $A_{2A}R$ antagonist KW6002 to enhance SWM may provide required preclinical data to facilitate the design of a clinical trial of $A_{2A}R$ antagonists for cognitive benefit in PD patients. Last, in squirrel monkeys trained to self-administer cannabinoids intravenously, the $A_{2A}R$ antagonists SCH-442416 and KW6002 produced a significant shift to the right and left, respectively, of the

cannabinoid self-administration dose-response curves (Justinova et al. 2014), paving the way for the development of $A_{2A}R$-based treatment for drug addiction.

15.7 Epidemiological and Animal Studies Support Pro-cognitive Effects of the Adenosine Receptor Antagonist Caffeine in Aging and Alzheimer's Disease

In the absence of an effective disease-modifying treatment to slow down or stop AD, epidemiological and experimental investigations of the potential risk factors (including dietary factors) that may allow individuals to decrease their risk for AD and improve cognitive symptoms have become compelling. Caffeine is doubtless the most widely consumed psychoactive substance by >50% of the world's adult population, largely for its psychostimulant (and cognitive enhancement) effect. At least seven longitudinal studies support an inverse relationship between caffeine consumption and decreased memory impairments associated with aging as well as a reduced risk of developing AD (for a review see Chen 2014), including the *Maastricht Aging Study* (van Boxtel et al. 2003; Hameleers et al. 2000), the *Canadian Study of Health and Aging (CSHA)* (Lindsay et al. 2002), the *FINE study* (van Gelder et al. 2007), the *French Three-City Study* (Ritchie et al. 2007), the *Cardiovascular Risk Factors, Aging, and Dementia (CAIDE) Study* (Eskelinen et al. 2009), and the *Honolulu-Asia Aging Study* (Gelber et al. 2011). For example, *the Honolulu-Asia Aging Study* involved 3494 men with a mean age 52 at cohort entry in 1965–1968 and found that the men in the highest quartile of caffeine intake were less likely than men in the lowest quartile to have any neuropathologic lesions at death in the 226 men with dementia and the 347 men with cognitive impairment who underwent brain autopsy (Gelber et al. 2011).

In further support of this inverse correlation between caffeine consumption and cognitive decline, animal studies show a causal role of caffeine in neuroprotection in animal models of AD: I) caffeine treatment reduced Aβ peptide-induced aggregation in cultured cerebellum granular cells and protected against loss of learning and memory induced by intracerebroventricular infusion of Aβ peptide (Canas et al. 2009a; Dall'igna et al. 2007; Espinosa et al. 2013) (210, 211, 220). II) Studies with aged AD transgenic (APPsw, Swedish mutation) mice found that long-term administration of a 1.5 mg daily dose of caffeine (equivalent to 500 mg in human) reduced brain Aβ levels and protected against certain cognitive impairments in 4–9-month-old APPsw mice; furthermore, in aged (18–19 months old) APPsw mice, which already exhibit decreased cognitive function, caffeine treatment enhanced working memory compared to non-treated APPsw mice (Cao et al. 2009; Arendash et al. 2006, 2009). III) Long-term oral caffeine treatment not only sustainably reduced plasma Aβ but also decreased both soluble and deposited Aβ in the hippocampus and cortex of aged AD mice (Cao et al. 2009). Intriguingly, caffeine's ability to improve cognitive performance in individual aged AD mice did not correlate with reduced plasma Aβ levels but was closely associated with the

reduced inflammatory cytokine levels in the hippocampus (Cao et al. 2009). In addition, caffeine acts at the neuronal $A_{2A}R$ to reverse cognitive impairments and associated synaptic dysfunction induced by chronic unpredictable stress (Kaster et al. 2015) and by depression-prone, hopeless mice (Machado et al. 2017).

This convergence of the epidemiological and animal evidence led to the proposal that caffeine might be a novel prophylactic agent to alleviate the burden of AD. The recent case-control study involving 124 total individuals provides the first direct evidence that caffeine/coffee intake is associated with a reduced risk of dementia (Cao et al. 2012). The study found that subjects with plasma caffeine levels greater than 1200 ng/ml at study onset were associated with stable MCI → MCI and no conversion to dementia during the 2–4-year follow-up examination (Cao et al. 2012). However, a very recent randomized control clinical trial of caffeine in PD has failed to confirm motor benefits with apparently exacerbated cognitive impairments (Postuma et al. 2017). Additional clinical studies are warranted to clarify this controversy and to test decisively the putative neuroprotective effects of caffeine in clinical trials in patients with AD.

15.8 Translational Potential of the Adenosine Receptor-Based Drugs for Controlling Cognitive Deficits in Neuropsychiatric Disorders

The convergence of clinical, epidemiological, and experimental evidence led to the proposal to translate the cognitive enhancement in rodents and nonhuman primates, and the safety profile of adenosine receptor, the $A_{2A}R$ antagonists, in particular, documented in clinical phase III trials in Parkinson's disease patients, to demonstrate the crucial ability of brain adenosine receptors (such as the $A_{2A}R$) to control cognitive deficits in neuropsychiatric disorders. Over the last 8 years, a total of 25 clinical trials have been conducted (for review see Chen et al. 2013). Six double-blind placebo-controlled clinical phase IIb and III trials of istradefylline (KW-6002) involving >2500 advanced PD patients and one phase IIb trial with preladenant (SCH420814) involving 253 PD patients were reported (Hauser et al. 2011). These clinical IIb and III trials have shown a modest but significant motor benefit: a reduction of the average "OFF" time by ~1.7 h compared to the "optimal" L-dopa dose regimen (Jenner et al. 2009); however, in 2008, the FDA found that efficacy results for motor benefits in these PD clinical trials were not sufficient, considered that this modest motor benefit was not sufficient to support the clinical utility of istradefylline. Additional PD clinical trials with istradefylline in Japan were undertaken to show consistent motor benefits, leading to the approval of istradefylline for treatment of PD in Japan in March 2013 (Dungo and Deeks 2013). Unfortunately, the effects of $A_{2A}R$ antagonists on cognition were not evaluated in these clinical trials. This is mostly due to the insufficient preclinical data on the ability of $A_{2A}R$ to control cognition – a knowledge gap that needs to be filled by future studies. Relevant

to drug discovery for cognitive improvement, these clinical IIb and III trials with the $A_{2A}R$ antagonists showed a very consistent and excellent safety profile in >3000 advanced PD patients (Hauser et al. 2011; Jenner et al. 2009). This safety profile of $A_{2A}R$ antagonists is entirely consistent with the widespread use of the nonselective adenosine receptor antagonist caffeine in 70% human population. Importantly, this provides an opportunity to translate rapidly $A_{2A}R$ antagonists to achieve cognitive improvement in neuropsychiatric disorders.

15.9 Summary

There is a convergence of molecular, animal, and epidemiological evidence suggesting that the $A_{2A}R$ and caffeine represent novel therapeutic strategies to improve cognitive impairments associated with neuropsychiatric disorders. The validity of this novel target is supported by the finding that $A_{2A}R$ antagonists and caffeine not only selectively enhance SWM, recognition memory, reversal learning, goal-directed behavior, Pavlovian conditioning, and effort-related behaviors in normal animals but also reverse SWM impairments in animal models of traumatic brain injury, PD, AD, schizophrenia, and HD. Pharmacological, genetic, and optogenetic studies coupled with well-controlled behavioral paradigms have revealed new insights into the mechanisms underlying AR control of cognition under physiological conditions (e.g., spatiotemporally precise integration of adenosine with dopamine and glutamate signaling, a common "break" mechanism by the striatopallidal $A_{2A}R$ to constrain cognition). Furthermore, $A_{2A}R$ inactivation reverses cognitive impairments in neurodegenerative disorders by blocking aberrantly increased $A_{2A}R$ signaling, by modifying aggregate protein processing, and by countering synaptopathy. Despite the converging animal and epidemiological evidence and the noted safety profiles of $A_{2A}R$ antagonists and caffeine, the therapeutic potential as well as the mechanism of $A_{2A}R$ antagonist effect on cognition in neuropsychiatric disorders remains to be established. Due to the insufficient preclinical data on this aspect, the effect of $A_{2A}R$ antagonists on cognition was not considered in these clinical PD trials. This may justify additional animal studies to better understand the mechanism underlying the $A_{2A}R$-mediated control of cognition in healthy brains (e.g., the permissive effect of AR, the spatiotemporal integration of adenosine/dopamine/glutamate signaling, and the selective control of distinct information processing phase). Further exploration of the molecular pathways whereby the adenosine receptor modifies degenerative proteins (such as phosphorylated Tau, α-synuclein, and β-amyloid) and prevents the early synaptic loss is critically needed. These studies may reveal the cellular and circuit mechanisms underlying the AR control of cognition and provide the required rationale to stimulate the necessary clinical investigation to translate rapidly $A_{2A}R$ antagonists and caffeine as novel strategies to control memory impairment associated with neuropsychiatry disorders.

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