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Striatopallidal adenosine A_{2A} receptor modulation of goal-directed behavior: Homeostatic control with cognitive flexibility

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Abstract

Dysfunction of goal-directed behaviors under stressful or pathological conditions results in impaired decision-making and loss of flexibility of thoughts and behaviors, which underlie behavioral deficits ranging from depression, obsessive-compulsive disorders and drug addiction. Tackling the neuromodulators fine-tuning this core behavioral element may facilitate the development of effective strategies to control these deficits present in multiple psychiatric disorders. The current investigation of goal-directed behaviors has concentrated on dopamine and glutamate signaling in the corticostriatal pathway. In accordance with the beneficial effects of caffeine intake on mood and cognitive dysfunction, we now propose that caffeine's main site of action - adenosine A_{2A} receptors ($A_{2A}R$) - represent a novel target to homeostatically control goal-directed behavior and cognitive flexibility. $A_{2A}R$ are abundantly expressed in striatopallidal neurons and colocalize and interact with dopamine D2, NMDA and metabotropic glutamate 5 receptors to integrate dopamine and glutamate signaling. Specifically, striatopallidal $A_{2A}R$ (i) exert an overall "break" control of a variety of cognitive processes, making $A_{2A}R$ antagonists a novel strategy for improving goal-directed behavior; (ii) confer homeostatic control of goal-directed behavior by acting at multiple sites with often opposite effects, to enhance cognitive flexibility; (iii) integrate dopamine and adenosine signaling through multimeric $A_{2A}R$-D_2R heterocomplexes allowing a temporally precise fine-tuning in response to local signaling changes. As the U.S. Food and Drug Administration recently approved the $A_{2A}R$ antagonist Nourianz® (istradefylline) to treat Parkinson's disease, striatal $A_{2A}R$-mediated control of goal-directed behavior may offer a new and real opportunity for improving deficits of goal-directed behavior and enhance cognitive flexibility under various neuropsychiatric conditions.

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Keywords

Adenosine A_{2A} receptor; Goal-directed behavior; Habit; Striatopallidal neurons; Homeostasis; Cognitive flexibility

1. Introduction

The basal ganglia critically gate multiple behaviors, ranging from locomotion, learning, emotion and cognition (Gunaydin and Kreitzer, 2016; Hikosaka et al., 2018). This involves multiple integrative modules organized as parallel striatal projection pathways that are driven by corticostriatal glutamatergic pathways (Cataldi et al., 2022; Lovinger, 2010). These circuits are fine-tuned by the dopamine and adenosine systems causing competitive and sometime opposite impacts on information flow to other brain regions. One type of striatum-dependent behavioral output/processing is the balance and smooth shift between goal-directed behaviors and habit formation (Cruz et al., 2023; Yin and Knowlton, 2006; Yin et al., 2008). Goal-directed behavior allows to continuously re-estimate circumstances adapting changes to reach a goal or avoid aversion; in contrast, habitual behavior triggers rapid responses to a particular stimulus or state that are resistant to interference (Dolan and Dayan, 2013; Smith and Graybiel, 2014). Their interaction and cooperation are critical for flexible and adaptive behaviors in our daily life.

The imbalance of goal-directed and habitual behaviors upon stressful or pathological conditions results in impaired decision-making, aberrant habitual behavior, increased stereotypy and behavioral disinhibition with loss of flexibility of thoughts (Robbins et al., 2019; Voon et al., 2017). Such deficits in goal-directed decision-making may therefore underlie disparate symptoms across psychiatric disorders, ranging from depression, obsessive-compulsive disorders (Gillan et al., 2011), drug addiction (Dolan and Dayan, 2013) and preservative behaviors seen in Huntington's (HD) or Parkinson's disease (PD) (Lawrence et al., 1998; Redgrave et al., 2010). Thus, the precise characterization of the fine-tuning of goal-directed behavior may contribute to cluster behavioral deficits across clinical diagnosis boundaries onto a common framework and facilitate the development of effective strategies to control goal-directed behavioral deficits across multiple psychiatric disorders.

Current investigation into the neuromodulation of goal-directed behaviors has largely concentrated on dopamine and glutamate signaling in the striatum (Yin and Knowlton, 2006). Dopamine and glutamate signaling formats multiple behavioral processes including prediction error signal, motivation, value and executive function: for example, nigrostriatal dopamine provides an "error prediction" signal for instrumental learning through reinforcement (Rossi et al., 2013; Steinberg et al., 2013) while the activation of the glutamatergic corticostriatal pathway exerts a "gain" control of cortical incoming information for action-outcome performance (Histed et al., 2009). Yet, these efforts have not translated into effective pharmacological strategies for improving deficits in goal-directed behavior. In fact, there is no effective pharmacological strategy to dampen deficits of goal-directed behavior in neuropsychiatric disorders.

This review focuses on new insights into the role of striatopallidal $A_{2A}R$ in temporal, cellular and circuit integration mechanisms conferring a homeostatic control of goal-directed behavior with enhanced cognitive flexibility. The formation of heteromers and signalosome complexes allows striatopallidal $A_{2A}R$ to temporally integrate dopamine and glutamate signaling to fine-tune striatal signaling and neuroplasticity. Moreover, the ability of striatopallidal $A_{2A}R$ to act as a break mechanism to constrain a variety of cognitive processes and to homeostatically control goal-directed/habitual behaviors with remarkable cognitive flexibility may provide a rationale to develop novel therapeutic strategies targeting $A_{2A}R$ to control deficits in goal-directed behavior in different psychiatric disorders.

2. Striatopallidal $A_{2A}R$ exert fine-tuning and temporally integrative modulation through signalosome complexes

$A_{2A}R$ are densely located in striatopallidal medium spiny neurons (MSN) (Fig. 1), where they colocalize and antagonistically interact with D_2R (Azdad et al., 2009; Hillion et al., 2002). $A_{2A}R$ also directly interact with NMDAR (Gerevich et al., 2002; Higley and Sabatini, 2010), mGlu5R (Ferré et al., 2002; Kachroo et al., 2005) and cannabinoid CB_1R (Carriba et al., 2007; Köfalvi et al., 2020) in a synergistic manner (Table 1). $A_{2A}R$ are also present at corticostriatal terminals (Hettinger et al., 2001; Rebola et al., 2005), where they modulate glutamate release (Ciruela et al., 2006; Rodrigues et al., 2005), controlling A_1R (Ciruela et al., 2006), CB_1R (Ferreira et al., 2015; Martire et al., 2011) and mGlu5R (Rodrigues et al., 2005). Thus, $A_{2A}R$ are uniquely positioned to integrate incoming information (glutamate signals) and neuronal sensitivity to this incoming information (dopamine signals) (Ferré et al., 2023) to control striatal synaptic plasticity (long-term depression - LTD and long-term potentiation - LTP) and different striatum-dependent behaviors including goal-directed behavior. Accordingly, $A_{2A}R$ modulate LTP at corticoaccumbal synapses (d'Alcantara et al., 2001) and LTP, LTD (Li et al., 2015a; Maltese et al., 2017; Morató et al., 2019) and spike-timing-dependent LTP (Flajolet et al., 2008; Shen et al., 2008a) at glutamatergic synapses onto striatopallidal MSN. Furthermore, concomitant stimulation of $A_{2A}R$ and D_2R shifts striatopallidal MSN plasticity from LTD to LTP (Shen et al., 2008a) and modulate a form of striatal LTD that is dependent on endocannabinoid release and D_2R activation (Kreitzer and Malenka, 2007). In particular, striatal LTD, which is restricted to striatopallidal MSN and requires activation of D_2R and mGlu5R (Kreitzer and Malenka, 2007; Lovinger, 2010), is the main form of synaptic plasticity in the dorsolateral striatum (DLS) (Di Filippo et al., 2009; Lovinger, 2010; Partridge et al., 2000). The loss of striatopallidal LTD is associated with a shift from goal-directed action (Furlong et al., 2017) to habitual responding (Nazzaro et al., 2012). Thus, striatopallidal $A_{2A}R$ signaling orchestrates D_2R-/mGlu5R-/CB_1R-mediated LTD in striatopallidal MSN to modify instrumental learning.

Among several $A_{2A}R$-dependent receptor-receptor interactions (Table 1), the homeostatic control of goal-directed (and other) behaviors by striatopallidal $A_{2A}R$ is mostly achieved by the strategic colocalization and formation of $A_{2A}R$-D_2R heteromers in the striatum (Ferré and Ciruela, 2019). $A_{2A}R$-D_2R heteromers have been studied extensively by fluorescence resonance energy transfer (FRET), receptor binding, co-immunoprecipitation and blocking peptides targeting the $A_{2A}R$-D_2R interaction site (Azdad et al., 2009; Hillion et al., 2002).

The presence of $A_{2A}R$-D_2R (Trifilieff et al., 2011) and $A_{2A}R$-CD73 heteromers in the intact striatum (Augusto et al., 2013) has been further confirmed by proximity ligation assays (PLA). The functional significance of these $A_{2A}R$-D_2R heteromers in intact animals is supported by the dynamic change of their relative density in different disease conditions, namely in the dopamine-depleted caudate-putamen after chronic L-DOPA treatment in non-human primates (Bonaventura et al., 2014), in the post-mortem brain of PD patients (Fernández-Dueñas et al., 2019), and their increased density (by nearly 2-fold) upon training to promote habit-based responses rather than training to promote goal-directed behavior (He et al., 2016).

Recent developments have allowed evolving from an initially proposed existence of different subpopulation (homomers *vs.* heteromers) of $A_{2A}R$ and D_2R in striatopallidal MSN to a revised model of a predominant population of $A_{2A}R$-D_2R heteromers forming molecular complexes with adenylyl cyclase subtype 5 (AC5), a major AC in striatal MSN (Navarro et al., 2018a), mGlu5R and CB_1R. These multimeric structures act as integrative devices of adenosine/dopamine/glutamate/endocannabinoid signals, dictating the excitability and gene expression pattern of striatopallidal MSN (Ferré et al., 2018). Furthermore, homeostatic control and integration of dopamine, glutamate, endocannabinoid and adenosine by these heteromeric signalossomes require co-stimulation of these receptors by the temporally precise arrival of these signals at striatopallidal MSN. Indeed, a recent study has revealed a temporally specific relationship between striatopallidal $A_{2A}R$ signaling and nigrostriatal dopamine signaling in association with the reward that is critical for the $A_{2A}R$ modulation of instrumental behavior (Li et al., 2016). Thus, this molecular and temporal integrative mechanism uniquely positions striatopallidal $A_{2A}R$ as preferential controllers of striatum-dependent behavior (including goal-directed behavior) to fine-tune distinct behavioral elements (such as the maintenance and retrieval of working memory) in response to local adenosine/dopamine signal changes.

In line with this molecular and physical signal integration, the contemporary theory of striatum-dependent behavioral learning postulates that the convergence of nigrostriatal dopamine (reinforcement) signal and corticostriatal glutamate (sensorimotor) signaling on striatopallidal MSN is critical for coding of the action and outcome relationship and instrumental behavior (Augustin et al., 2014; Yagishita et al., 2014). Striatopallidal $A_{2A}R$ may modulate instrumental learning by acting precisely at the time of the reward to interact with the reward-triggered dopamine and glutamate signaling. The temporal tight relation between $A_{2A}R$ signaling and the reward-triggered dopamine and glutamate signaling in the control of instrumental behaviors was recently highlighted using opto$A_{2A}R$ (Li et al., 2015b): the time-precise optogenetic control of intracellular $A_{2A}R$ signaling showed that a transient and “time-locked” (but not random) activation of striatopallidal MSN at the time of the reward is sufficient to affect acquisition of instrumental behaviors and to define the animal’s sensitivity to goal-directed valuation (Li et al., 2016). This conclusion is in agreement with a recent study showing the precision and sufficiency of “time-locked” activation of the striatopallidal pathway during the reward to modify instrumental learning and with the recent optogenetic identification of a narrow (0.3–2 s) critical time window for modulation of striatal plasticity after optogenetic stimulation of nigrostriatal dopamine and corticostriatal glutamate inputs separately (Yagishita et al., 2014).

3. Striatopallidal $A_{2A}R$ act as a "break" mechanism constraining cognition

Increasing evidence from diverse learning paradigms suggest that the activation of striatopallidal $A_{2A}R$ exerts a selective inhibitory control on various cognitive behaviors, including working memory (Augusto et al., 2013; Li et al., 2018a), instrumental learning (Li et al., 2016, 2018a), reversal learning and set-shifting (Zhou et al., 2019), Pavlovian fear conditioning (Wei et al., 2014), and goal-directed behavior (Emtage et al., 2022; Li et al., 2016, 2018b). Thus, the comparison of global, forebrain-specific and striatum-specific $A_{2A}R$ knockout (KO) models shows that the inactivation of striatal $A_{2A}R$ is sufficient to enhance a variety of cognitive processes including working memory (Wei et al., 2011), reversal learning (Wei et al., 2011), goal-directed behavior (Yu et al., 2009), Pavlovian fear conditioning (Wei et al., 2014), effort-related decision making and effort expenditure (Mingote et al., 2008; Sun et al., 2023) without affecting spatial reference memory, motor function, and anxiety-like behaviors in 'control' rodents.

Instrumental behaviors are operationally defined as behavioral responses that are sensitive (goal-directed) or insensitive (habit) to outcome value and action-outcome contingency (Redgrave et al., 2010; Yin and Knowlton, 2006). The devaluation test reveals that striatum-specific $A_{2A}R$ KO mice or focal $A_{2A}R$ KO in the dorsomedial striatum enhance goal-directed behavior; conversely, optogenetic or chemogenetic activation of striatopallidal neurons in the dorsomedial striatum suppress goal-directed behavior (He et al., 2020). However, goal-directed and habitual behaviors may at times compete and at others cooperate in the selection and subsequent evaluation of actions because their control over performance appears to be all or none (Balleine and Dezfouli, 2019). The critical issue is whether striatopallidal $A_{2A}R$ preferentially control goal-directed behavior at the expense of habit formation or *vice versa* or both, an issue that cannot be addressed by standard random ratio (RR, promoting goal-directed behavior) or random interval (RI, promoting habit formation) training protocols since the devaluation test would produce an all or none response without delineating their relationship. We have recently clarified this issue using the RR and RI dual trainings in the morning and afternoon respectively for 10 days, which allowed demonstrating that $A_{2A}R$ in the nucleus accumbens (NAc) preferentially control goal-directed behavior (Li et al., 2020). Importantly, the goal-directed consequence of striatopallidal $A_{2A}R$ inactivation should be attributed to an enhanced goal-directed behavior but can be manifested as an impaired habit formation (Yu et al., 2009). This preferential modulation of goal-directed compared to habit-based learning by $A_{2A}R$ was further confirmed by the ability of $A_{2A}R$ blockade to selectively reverse goal-directed behavior triggered by aggregated α-synuclein in the striatum (He et al., 2022).

It should be noted that the over-inhibition of $A_{2A}R$ may potentiate goal-directed drug seeking behaviors such as alcohol consumption as indicated by genetic or pharmacological inactivation of $A_{2A}R$ (Nam et al., 2013). Consistently, $A_{2A}R$ agonists or the direct activation of $A_{2A}R$-containing MSN of the indirect pathway in the dorsomedial striatum decreases conditioned alcohol-seeking behaviors (Hong et al., 2019), although $A_{2A}R$ inhibition promotes an orbitofrontal-DMS LTP that reduces alcohol-seeking behaviors (Cheng et al., 2021). These studies highlight the importance of the contexts of establishment of goal-directed behaviors. More precisely, $A_{2A}R$ antagonism may mediate both enhanced cognitive

beneficial goal-directed behaviors and maladaptive detrimental goal-directed behaviors such as addictive behaviors, depending on when and in what contexts the $A_{2A}R$ inactivation occurs.

The “brake”/inhibitory control by striatopallidal $A_{2A}R$ is apparently inconsistent with a proposal that the D_1R-expressing direct pathway selectively controls reward behavior while the indirect pathway selectively controls aversive behavior such as fear conditioning (Hikida et al., 2013). This proposal is based on the finding that selectively blocking striatopallidal neurons attenuates aversive learning (i.e. electric shock-induced fear conditioning) but has no effect on reward behavior (e.g. cocaine-induced place preference conditioning) and that the $A_{2A}R$ antagonist SCH58261 attenuates Pavlovian fear conditioning (Hikida et al., 2013). However, brain-region specific $A_{2A}R$ KO mice allowed showing that the selective deletion of striatal $A_{2A}R$ enhances fear conditioning while forebrain $A_{2A}R$ (including the cortex, hippocampus and striatum) attenuate fear conditioning (Wei et al., 2014). Thus, the attenuation of fear conditioning by $A_{2A}R$ antagonists likely results from an action of cortical or amygdala $A_{2A}R$ (Simões et al., 2016), rather than striatopallidal $A_{2A}R$. This would argue against a selective involvement of the indirect pathway, which promotes aversive behaviors, but supports the view that the activation of the indirect pathway inhibits fear conditioning.

Taken together, striatopallidal $A_{2A}R$ assume *a common inhibitory* control over diverse cognitive processes and thus function as a common "break" mechanism to constrain cognition. These findings not only herald the notion that the suppression of $A_{2A}R$ activity is pro-cognitive but also support the possibility that $A_{2A}R$ may be a target for selectively alleviating cognitive deficits in pathological conditions (see below). The control of cognition by striatopallidal $A_{2A}R$ is consistent with the critical role of striatopallidal MSN in instrumental learning as revealed by a series of studies with the deletion of Gpr6 (a striatopallidal-enriched gene) (Lobo et al., 2007), optogenetic stimulation of D_2R-containing neurons (Kravitz et al., 2012; Tai et al., 2012) and enhanced glutamatergic synaptic transmission in striatopallidal MSN of the dorsolateral striatum (Yin et al., 2009).

The classic model of the basal ganglia predicts that experimental manipulations of the striatopallidal pathway with pharmacological, lesioning, genetic knockout and optogenetic approaches would produce a pronounced effect on motor activity (Carvalho Poyraz et al., 2016; Durieux et al., 2009). Altered motor activity would confound the dissection of the causal role of striatopallidal $A_{2A}R$ in the control of goal-directed and habitual behaviors. However, the use of brief light stimulation parameters in the instrumental training sessions (i.e. 10 mW, 2 s occurring randomly within 1 min) and the use of a behavioral paradigm whose main readout is performance accuracy (which is largely independent of motor activity), allow demonstrating that striatopallidal $A_{2A}R$-mediated inhibitory control is largely independent of confounding motor activity.

As all behaviors are operated on the top of an arousal effect, this “break” mechanism may also be associated with the ability of striatopallidal $A_{2A}R$ to modulate arousal (Lazarus et al., 2012) and enhanced motivation (He et al., 2020). Indeed, $A_{2A}R$ play a crucial role in the regulation of sleep (Huang et al., 2005; Lazarus et al., 2011), and $A_{2A}R$ in the NAc mediates the arousal effect of caffeine, a non-specific antagonist of A_1R and $A_{2A}R$

(Lazarus et al., 2011). Interestingly, a recent study has identified a broad distribution of striatopallidal projections in the forebrain, diencephalon, and brainstem (Zhang et al., 2013), including the densest projection to the lateral hypothalamus (containing orexin/hypocretin) which can activate noradrenergic cells of the locus coeruleus, dopaminergic cells of the ventral tegmental area, serotonergic cells of the dorsal raphe, and histaminergic cells of the tuberomammillary nucleus, all of which cause arousal from sleep (Sakurai, 2007) (see Fig. 1). Meanwhile, sleep disorders impair cognitive function and caffeine exerts its wake-promoting effect by blockade of $A_{2A}R$ (Huang et al., 2005). Therefore, it is of great interest to investigate if and how the ability of $A_{2A}R$ to regulating sleep-wake cycle may be paramount to modulate inhibitory control and cognition.

3.1. Striatopallidal $A_{2A}R$ confer an homeostatic control of cognition

Importantly, despite its overall "break" control of cognition, striatopallidal $A_{2A}R$ confer a unique ability for homeostatic control of goal-directed behavior with enhanced cognitive flexibility. The neuromodulation role of adenosine is tightly associated with cellular ATP metabolism and purine synthesis. The production of adenosine results from an enhanced ATP breakdown under metabolically unfavorable conditions such as stress, hypoxia or inflammation. By acting at multiple receptors (such as $A_{2A}R$), adenosine functions as a retaliatory metabolite to restore tissue homeostasis (Cunha, 2001), with a particular relevance in brain tissue, where $A_{2A}R$ are key mediators of synaptic stability in neuronal circuits (Gomez-Castro et al., 2021; Xu et al., 2022). Indeed, $A_{2A}R$ are part of a homeostatic control mechanism of cognition and behavioral inhibition by simultaneously acting at multiple sites with opposite effects. For example, $A_{2A}R$ located in different striatopallidal MSN differently affect goal-directed and habitual actions: the bidirectional manipulation of striatopallidal $A_{2A}R$ by optogenetic activation of $A_{2A}R$ signaling and Cre-mediated knockdown, unambiguously shows that the inactivation of $A_{2A}R$ in the dorsomedial striatum (DMS) and dorsolateral striatum (DLS) specifically enhances goal-directed and habitual actions, respectively (Li et al., 2016). The reciprocal competing and inhibitory control of the striatopallidal pathway in the DMS and DLS may be attributed to their distinct time-dependent plasticity (Perez et al., 2022) and their distinct corticostriatal networks, with DMS mainly receiving projections from medial prefrontal cortex (associative network) that encodes action-outcome contingency for goal-directed behavior while the DLS mostly receives projections from the motor cortex (sensorimotor network) that encodes stimulus-response relationship for habitual behavior (Balleine et al., 2009; Yin and Knowlton, 2004). Furthermore, $A_{2A}R$ in presynaptic and postsynaptic elements of the corticostriatal synapse have an opposite impact on spatial working memory and psychomotor activity (Shen et al., 2008b) as well as on fear conditioning (Wei et al., 2014) and cocaine-induced DARPP-32 phosphorylation and c-Fos expression (Shen et al., 2013). Moreover, $A_{2A}R$ in striatopallidal neural bodies of NAc and output projection terminals of ventral pallidum exert an opposite effect on Pavlovian conditioning (Li et al., 2020), the former depressing and the later facilitating Pavlovian-to-instrumental transfer. Decision-making is also oppositely controlled by striatal $A_{2A}R$ (Clissold and Pratt, 2014; Salamone et al., 2018; Yu et al., 2009) and by prefrontocortical $A_{2A}R$ (Leffa et al., 2018), which exert inhibitory and facilitatory effects, respectively. Likewise, cognition is also under parallel control by striatal and hippocampal $A_{2A}R$ (Carvalho et al., 2019; Viana da Silva et al., 2016; Temido-Ferreira

et al., 2020). In addition, neuronal and astrocytic $A_{2A}R$ have opposite modulatory effects on working memory and MK-801-induced psychomotor activity since the blockade of neuronal $A_{2A}R$ promotes whereas astrocytic $A_{2A}R$ attenuates the efficiency of these behavioral outputs (Matos et al., 2015). Collectively, by multiple and often opposite actions of $A_{2A}R$ at different locus of striatopallidal $A_{2A}R$-containing neurons (corticostriatal inputs or striatopallidal projections), $A_{2A}R$ signaling may reciprocally inhibit (and occasionally synergize) to modulate the final output pathway, in line with the interconnected self-control of striatal circuits (Gremel and Costa, 2013; Redgrave et al., 2010) (Fig. 2). This multiple action (like "Swiss-army") feature prevents extreme behaviors and facilitates the smooth shifting between different types of behaviors. The parallel control over goal-directed and habitual actions exerted by striatopallidal MSN in DMS and DLS, striatal *vs.* cortical/hippocampal, striatopallidal neuronal bodies *vs.* striatopallidal projections, or astrocytes *vs.* neurons, all endow a unique balance to smoothly switch between goal-directed and habitual action for maximized behavioral performance.

This homeostatic control of goal-directed behavior by $A_{2A}R$ signaling may constrain behavior processes from reaching extreme values: this allostatic property of striatopallidal $A_{2A}R$ may enforce rigidity control (either goal-directed or habit) and may underlie the ability of striatopallidal $A_{2A}R$ antagonism to preferentially enhance cognitive flexibility. Indeed, exploiting the Cre-loxP-mediated focal knockdown of $A_{2A}R$ in the DMS and NAc, allowed demonstrating that the knockdown of $A_{2A}R$ selectively in the NAc enhances cognitive flexibility by increasing set-shifting as well as reversal learning (Li et al., 2020; Zhou et al., 2019). While the reduced number of regressive errors facilitates a new strategy in the set-shifting phase, the suppression of the preservative errors inhibits the previous strategy in the reversal phase. These two distinct processes suggest that NAc $A_{2A}R$ dually control cognitive flexibility by distinctly controlling different glutamatergic inputs into the NAc, from medial prefrontal cortical and orbitofrontal cortex, respectively (Birrell and Brown, 2000; Cui et al., 2018; McAlonan and Brown, 2003). Thus, the knockdown of NAc $A_{2A}R$ selectively improves attentional set-shifting by increasing the ability of learning and maintaining the new extradimensional strategy (Li et al., 2020; Zhou et al., 2019). This view is also consistent with the observations that $A_{2A}R$ KO enhances strategy shifting in the water maze paradigm (Wei et al., 2011), and that treatment with caffeine (a non-selective $A_{2A}R$ antagonist) significantly improves attention and cognitive deficits in an animal model of attention deficit and hyperactivity disorder (Pandolfo et al., 2013). Collectively, these findings suggest that the blockade of NAc $A_{2A}R$ enhances cognitive flexibility and thereby increases learning ability by maintaining a new extradimensional strategy and possibly inhibiting the old intradimensional old strategy. This is consistent with reports showing that inactivation of the NAc enhances learning of irrelevant stimuli in a set-shifting assay (Floresco et al., 2006; Jongen-Rêlo et al., 2002; Tai et al., 1995). Notably, this increased flexibility upon $A_{2A}R$ blockade is self-controlled, based on the opposite impact of striatopallidal and prefrontocortical $A_{2A}R$ in the control of decision-making (Leffa et al., 2018). This simultaneously emphasizes the overall ability of $A_{2A}R$ antagonists to increase behavioral flexibility, together with the overall homeostatic role of the adenosine modulation system (Cunha, 2001, 2016), with $A_{2A}R$ in different brain regions exerting opposite self-limiting effects on this behavioral flexibility, as has been reported for the

$A_{2A}R$-mediated control of different brain functions such as schizophrenia, psychomotor activity or fear memory (Matos et al., 2015; Shen et al., 2008b; Wei et al., 2014).

3.2. Targeting striatopallidal A2aR for improving cognitive deficits in neuropsychiatric disorders

This presently proposed key role of striatopallidal $A_{2A}R$ in inhibitory control acting as a 'brake' of cognition, entails the possibilities that the abnormal function of striatopallidal $A_{2A}R$ may be a causative factor for the onset of decision-making-related symptoms in different neuropsychiatric diseases and that $A_{2A}R$ antagonists may correct these behavior abnormalities. Indeed, animal studies have been paramount to support the preclinical utility of $A_{2A}R$ antagonists to control dysfunctions of cognition and inhibitory control in different brain disease models (reviewed Chen, 2014; Cunha, 2016). Thus, $A_{2A}R$ antagonists attenuate working memory impairments in animal models of PD (Carmo et al., 2019; Kadowaki Horita et al., 2013; Li et al., 2018a), HD (Li et al., 2015a), traumatic brain injury (Ning et al., 2013; Zeng et al., 2020), Alzheimer's disease (AD) (Canas et al., 2009) as well as upon repeated stress (Kaster et al., 2015). Importantly, the benefits resulting from $A_{2A}R$ antagonism may be selective and long-lasting under brain pathological conditions, since the onset of brain dysfunction or noxious brain conditions is characterized by an upregulation of $A_{2A}R$ (reviewed in Cunha, 2016) and an overactivation of $A_{2A}R$ signaling in the brain (Canas et al., 2018; Carmo et al., 2019; Gonçalves et al., 2019,2022; Meng et al., 2019). In fact, $A_{2A}R$ overfunction is sufficient to trigger memory dysfunction (Li et al., 2015b; Pagnussat et al., 2015) and the overexpression of $A_{2A}R$ seems paramount to bolster the susceptibility to memory dysfunction (Carvalho et al., 2019; Temido-Ferreira et al., 2020). Conversely, the genetic or pharmacological inactivation of $A_{2A}R$ attenuates memory impairments in aging (Prediger et al., 2005a) and in disease models of AD (Carvalho et al., 2019; Dall'Igna et al., 2007; Gonçalves et al., 2019; Laurent et al., 2016; Viana da Silva et al., 2016), chemotherapy-induced cognitive impairment (Oliveros et al., 2022), propofol-anesthesia-induced loss of consciousness (Guo et al., 2022), childhood convulsions (Cognato et al., 2010) and attention deficit and hyperactivity disorder (Prediger et al., 2005b), through a control of the dysfunction of glutamatergic synapses (Canas et al., 2018; Gonçalves et al., 2019; Kaster et al., 2015; Laurent et al., 2016; Silva et al., 2018; Temido-Ferreira et al., 2020; Viana da Silva et al., 2016). The relation between $A_{2A}R$ and memory performance is further strengthened by the observations of an association between $A_{2A}R$ polymorphisms with Alzheimer' disease (Siokas et al., 2022), pre-attentive visual sensory memory subprocesses (Beste et al., 2012), attentional domains of executive control (Renda et al., 2015) and memory dysfunction in mild cognitive impairment (Horgusluoglu-Moloch et al., 2017). The presently proposed central hypothesis that $A_{2A}R$ in striatopallidal neurons are a likely target for therapies aimed at alleviating cognitive deficits, implies 3 mechanistic working hypotheses: i) $A_{2A}R$ in striatopallidal neurons functions as a "brake" mechanism in the control of working memory and goal-direct behavior; ii) the indirect pathway in distinct striatal subregions or prefrontal cortex and hippocampus control distinct cognitive domains; iii) the inactivation of $A_{2A}R$ in the ventral striatum prevents cognitive impairments by dopamine overdosing. These working hypotheses are novel, and their validation will foster a new level of understanding of striatal learning and are crucial to guide the design

of clinical trial of $A_{2A}R$ antagonists for cognitive amelioration in different neuropsychiatric diseases.

The “brake” mechanism operated by striatopallidal $A_{2A}R$ also entails that the removal of this “break” mechanism by striatopallidal $A_{2A}R$ antagonism is a promising therapeutic strategy to foster a recovery from maladaptive habitual addictive or obsessive-compulsive disorders. This contrasts with most studies with pharmacological and genetic manipulation of neuromodulators (with the exception of the D_1R agonists; Haluk and Floresco, 2009) and focal lesioning, which often disrupt normal behavior and impair cognitive flexibility (Ding et al., 2014; Grospe et al., 2018; Parikh et al., 2016). The potential to exploit $A_{2A}R$ antagonists for amelioration of neurobehavioral deficits in human cocaine addicts is highlighted by a recent functional MRI study showing greater activation of the orbitofrontal cortex upon treatment with the $A_{2A}R$ antagonist SYN115 in cocaine dependent subjects (Moeller et al., 2012) and by the increase of D_2R/D_3R density in the striatum after exposure to caffeine (a non-selective adenosine receptor antagonist) in humans (Volkow et al., 2015), although $A_{2A}R$ were not effective in some animal models of post-cocaine working memory deficits (Hámor et al., 2020). However, $A_{2A}R$ antagonism alleviated multiple symptoms of quinpirole-induced psychosis by rescuing abnormal excitatory synaptic function in MSN of the indirect pathway of sensitized mice (Asaoka et al., 2019). Indeed, polymorphisms of the $A_{2A}R$ gene seem to be a vulnerability factor for methamphetamine dependence/psychosis, especially in females (Kobayashi et al., 2010). Also, both the association of polymorphisms of the $A_{2A}R$ gene with major depression (Oliveira et al., 2019) and anxiety (Alsene et al., 2003; Domschke et al., 2012; Hohoff et al., 2010), as well as epidemiological studies linking the consumption of caffeine with a reduced incidence of depression (Grosso et al., 2016; Kim and Kim, 2018; Kimura et al., 2020; Lucas et al., 2011; Navarro et al., 2018b) and studies in chronically stressed mice (Kaster et al., 2015; Zhu et al., 2022) have converged to the conclusion that $A_{2A}R$ control mood. Chronic stress shifts behavioral control from goal-directed toward habitual strategy (Radenbach et al., 2015), mainly through a frontostriatal reorganization involving DMS and NAc circuits (Dias-Ferreira et al., 2009; Taylor et al., 2014). The dysfunction of this behavioral control strategy may contribute to the pathogenesis of obsessive-compulsive disorder (Adams et al., 2018) and addiction (Dolan and Dayan, 2013). Importantly, caffeine and $A_{2A}R$ selective antagonists can prevent mood and memory dysfunction triggered by chronic stress (Kaster et al., 2015). Thus, it can be speculated that $A_{2A}R$ signaling in NAc might modulate the dysfunction of decision-making triggered by mood-related behavior, which need to be further examined. Careful clinical study designs for testing mood and cognitive impairments that are not confounded by changes in motor behavior and sensitivity to reward are needed to confirm the validity of targeting striatopallidal $A_{2A}R$ as an effective therapy for improving mood and cognitive impairments under neuropsychiatric conditions.

Finally, it is expected that the study of striatal $A_{2A}R$ in the control of cognition in humans may soon be feasible. Indeed, the U.S. Food and Drug Administration (FDA) approved the $A_{2A}R$ antagonist Nourianz (istradefylline) for treatment of PD with "off" episodes on August 27, 2019 (Chen and Cunha, 2020). This opens a new repurposing opportunity for pharmacological control of goal-directed behavior. However, the effect of istradefylline on cognition was not probed in the clinical trials testing $A_{2A}R$ antagonists in PD patients.

With the approval of istradefylline, it will now be possible to evaluate the ability of $A_{2A}R$ antagonists to reverse cognitive deficits in PD patients in phase IV trials (Chen and Cunha, 2020).

4. Conclusions

The distinct features of striatopallidal $A_{2A}R$ to fine-tune dopamine and glutamate signaling by a conjunction of direct intramembrane receptor-receptor interaction and temporal integrative properties, enables striatopallidal $A_{2A}R$ to act as a "break" mechanism to constrain a variety of cognitive behaviors involving modulation of the arousal system as well as to confer homeostatic control of goal-directed/habitual behaviors with enhanced cognitive flexibility by acting at multiple circuit sites and behavioral elements. Overall, these properties prompt considering striatopallidal $A_{2A}R$ as novel and promising targets to modulate goal-directed behavior and cognitive flexibility. The translational potential of the pharmacological blockade of striatopallidal $A_{2A}R$ is further enhanced by the recent FDA approval of the $A_{2A}R$ antagonist istradefylline for PD treatment which opens up a new and real possibility to improve the deficits in goal-directed behavior that underlie these seemingly disparate symptoms across psychiatric disorders.

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Abbreviations:

AC	adenylyl cyclase
AD	Alzheimer's disease
DLS	dorsolateral striatum
DMS	dorsomedial striatum
HD	Huntington's disease
KO	knockout
LTD	long-term depression
LTP	long-term potentiation
mPFC	medium prefrontal cortex
MSN	medium spiny neurons

NAc	nucleus accumbens
PD	Parkinson's disease
RI	random interval
RR	random ratio

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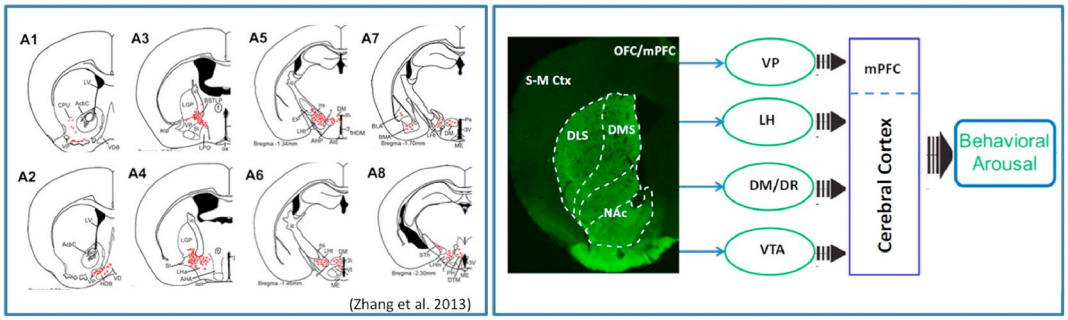

Regions	Varicosities	Terminal networks	Regions	Varicosities	Terminal networks	Regions	Varicosities	Terminal networks
Forebrain			**Diencephalon**			VTM	47	+
BST	–	–	LPO	212	+++	DTM	64	±
BSTLP	267	++	LHa	936	++++	STh	96	++
VP	998	++++	LHt	2023	++++	**Brainstem**		
VDB	189	+	LHm	334	+++	VTA	295	+++
HDB	126	++	AHP	423	+++	MnR	244	++
BMA	433	++	Pe	138	±	DR	278	++
BLA	423	++	DM	1228	+++	VLPAG	127	+
CPU	38	+	EP	33	+	DRI	–	–
SI	272	+++	VMHDM	822	++	MPB	–	–
LGP	187	+++	PH	244	++	LC	–	–

(Zhang et al. 2013)

Fig. 1.

Broad distribution of striatopallidal projections in the forebrain, diencephalon and brainstem, including the lateral hypothalamus, ventral tegmental area and dorsal raphe, all of which cause behavioral arousal. OFC/mPFC: orbital frontal cortex/medium prefrontal cortex; S-M Ctx: sensory motor cortex; DMS: dorsomedial striatum; DLS: dorsolateral striatum; NAc: nucleus accumbens.

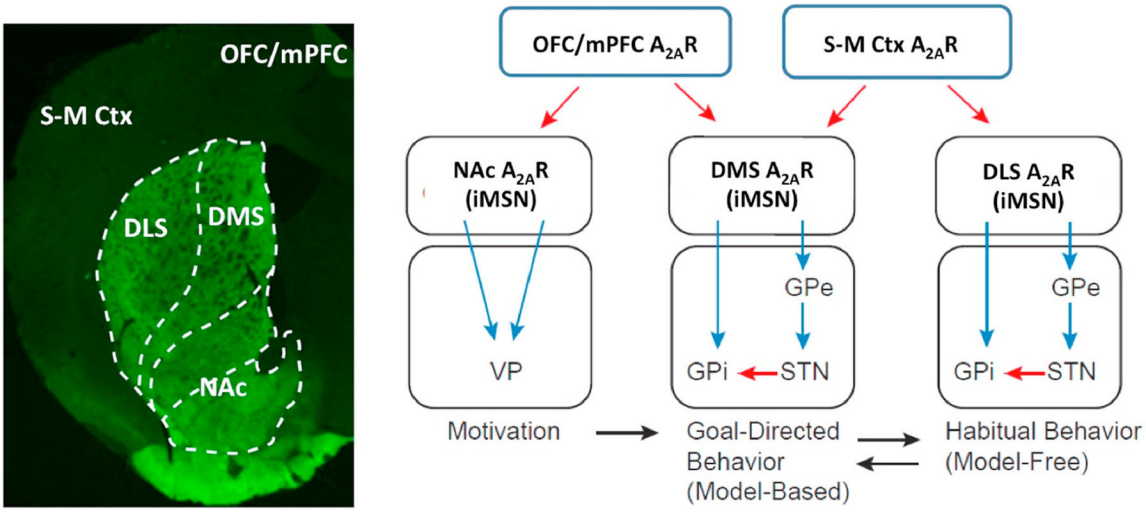

Fig. 2.

Different striatal subregions (DMS: dorsomedial striatum; DLS: dorsolateral striatum; NAc: nucleus accumbens) with the connecting cortical regions subserve distinct cognitive elements of goal-directed and habitual behaviors.

Table 1

Receptor-Receptor (R-R) Interaction of the $A_{2A}R$ with GPCRs and ectonucleotidase.

R-R Interaction	Main Findings	References
$A_{2A}R$-D_2R	Opposing action of $A_{2A}R$ agonist on D_2R Evidence for R-R interaction by FRET and BRET in cells	Ferré et al., 1991 Canals et al., 2003
	$A_{2A}R$ agonist decreases D_2R affinity dopamine in human striatum	Díaz-Cabiale et al., 2001
$A_{2A}R$-D_3R	Antagonistic interaction between $A_{2A}R$ and D_3R	Torvinen et al., 2005
$A_{2A}R$-mGluR5	Synergistic interaction between $A_{2A}R$ and mGluR5	Ferré et al., 2002
	R-R in the hippocampus	Tebano et al., 2005
	R-R in the striatum	Rodrigues et al., 2005
$A_{2A}R$-CB1	R-R in the striatal glutamatergic neurotransmission	Martire et al., 2011
	R-R in the dorsal striatum	Moreno et al., 2018
	R-R in the hippocampus and alters THC-induced cognitive impairment	Aso et al., 2019
$A_{2A}R$-CD73	Synergistic interaction between $A_{2A}R$ and CD73, an ecto-nucleotidase	Augusto et al., 2013