REVIEW

Effects of caffeine on striatal neurotransmission: Focus on cannabinoid CB1 receptors

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Caffeine is the most commonly self-administered psychoactive substance worldwide. At usual doses, the effects of caffeine on vigilance, attention, mood and arousal largely depend on the modulation of central adenosine receptors. The present review article describes the action of caffeine within the striatum, to provide a possible molecular mechanism at the basis of the psychomotor and reinforcing properties of this pharmacological agent. The striatum is in fact a subcortical area involved in sensorimotor, cognitive, and emotional processes, and recent experimental findings showed that chronic caffeine consumption enhances the sensitivity of striatal GABAergic synapses to the stimulation of cannabinoid CB1 receptors. The endocannabinoid system is involved in the psychoactive effects of many compounds, and adenosine A2A receptors (the main receptor target of caffeine) elicit a permissive effect towards CB1 receptors, thus suggesting that A2A-CB1 receptor interaction plays a major role in the generation and maintenance of caffeine reinforcing behavior. Aim of this review is to describe the effects of caffeine on striatal neurotransmission with special reference to the modulation of the endocannabinoid system.

Keywords:
Adenosine / IPSC / Psychostimulant / Reward / Stress

1 Introduction

Caffeine is the most widely consumed psychoactive substance in the world. It is contained in coffee, tea, soft drinks and chocolate. The cardiovascular and central stimulant properties of caffeine have been known for decades. Overall, the psychostimulant properties are due to its ability to affect neurotransmission in different brain regions, promoting motor activity, attention and vigilance [1]. Among these behavioral effects, the enhancement of motor activity produced by caffeine has recently received a great deal of attention. Compared to other potent psychostimulants, such as cocaine or amphetamine, caffeine is a weak reinforcing drug [2], but dependence and withdrawal [3], as well as cases of abuse have also been reported with caffeine in humans [4, 5]. These events could potentially increase in the future, due to the current diffusion of ''energy drinks'' containing high concentrations of caffeine [5–8]. The aim of this review article is to describe the molecular mechanism underlying the central effects of caffeine, with special reference to its action in the nucleus striatum, a brain structure involved in the control of motor, cognitive and emotional functions [9–12], and involved in psychostimulant addiction [13, 14].

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Abbreviations: DARPP-32, dopamine and cAMP-regulated phosphoprotein of 32 kDa; **PKA,** protein kinase

Recent findings suggested a caffeine–endocannabinoid system interaction in the striatum [15], similar to what is observed with classical substances of abuse [16–18].

The endocannabinoids, endogenous ligands of the cannabinoid receptors, are synthesized ''on demand'' in response to increased neuronal excitation and act in a retrograde manner to activate the presynaptic CB1 receptors and to inhibit neurotransmitter release at both excitatory and inhibitory synapses [19, 20]. The altered regulation of these synapses has been shown to contribute to the central effects of caffeine exposure and is discussed in this article. The potential therapeutic significance of caffeine-induced neuromodulation in conditions affecting striatal neurotransmission is also discussed.

2 Mechanism of action

In the central nervous system, caffeine has many potential biochemical effects, but it appears that in the doses regularly consumed by humans, its main pharmacological targets are the adenosine receptors (Fig. 1). Caffeine acts as a competitive antagonist of these receptors, showing the same affinity for both A1 and A2A subtypes, which appear to be the most likely targets under normal physiological conditions [3]. When acutely administered, caffeine effects are predominant on A1 receptors, since these receptors are preferentially activated by ambient adenosine [21]. Chronic caffeine consumption, however, results in the tolerance of A1 receptors to caffeine [22], so that in this condition the effects of caffeine on A1 receptors are negligible, and its action on A2A receptors becomes prevalent [21].

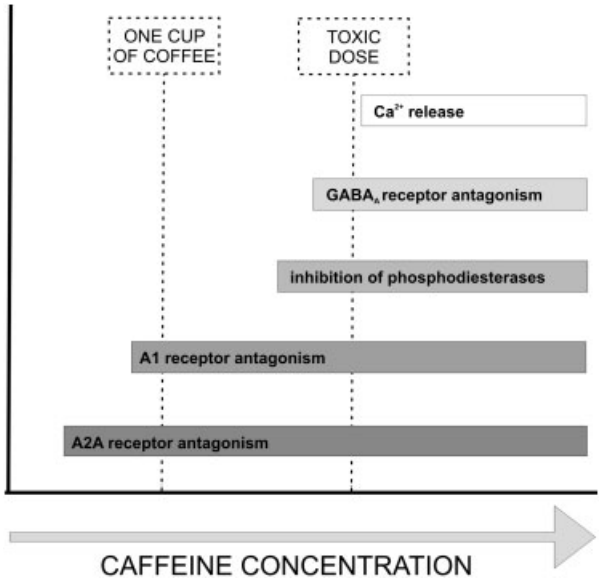

Figure 1. Concentration-dependent effects of caffeine on adenosine receptors, phosphodiesterases, GABA receptors and calcium release.

Adenosine A1 receptors are preferentially expressed on presynaptic terminals, where they tonically inhibit neurotransmitter release through the reduction of cyclic AMP levels [1]. Caffeine can enhance the release of neurotransmitters by abolishing such inhibitory control, as described for acetylcholine in the hippocampus [23] and in the prefrontal cortex [24]. Furthermore, caffeine can regulate the A1 receptor-mediated activation of potassium channels and, finally, the firing of many central neurons [25]. On the other hand, the A2A receptors are mainly present in the striatum on dendritic spines, where they inhibit glutamatergic thalamo-cortical neurones by inducing cell activation and stimulating adenylate cyclase pathway. Caffeine, by blocking A2A receptors, decreases the stimulatory action on cyclic AMP levels physiologically induced by adenosine [1] (Fig. 2).

Only at toxic doses, caffeine could have many other potential molecular targets, since it modulates calcium release from intracellular stores [6], phosphodiesterase activity [26], GABAA receptors [27], and also protein kinase C activity [28] (Fig. 1).

3 Effects on striatal neurotransmission

The basal ganglia form a subcortical station where information coming from the cortex is collected, integrated and then sent back to modulate motor programs and cognitive processes. The striatum is the main receiving area of the basal ganglia, mostly consisting of GABAergic medium spiny neurons, which account for the 95% of its population. These cells receive glutamatergic excitatory input from the cortex, GABAergic inhibitory input from axon collaterals and striatal interneurons and modulatory input from midbrain dopaminergic neurons. Interaction between these inputs controls the output of the striatum to the substantia nigra and globus pallidus [29].

Increasing evidence indicates that caffeine can affect the activity of striatal projection neurons. In particular, it can reduce the inhibition exerted by endogenous adenosine on striatal dopamine transmission, reducing the activity of striatal neurons and ultimately disinhibiting thalamo-cortical projection neurons. In fact, a complex antagonistic relationship between adenosine A2A and dopamine D2 receptors is described at the level of striatal neurotransmission [11].

The activation of A2A receptors reduces the affinity of D2 receptors for agonists [30] and results in G protein-dependent stimulation of cAMP production, whereas activation of D2 receptors decreases the production of cAMP. This leads to opposite regulation of the activity of cAMP-dependent protein kinase (PKA) which, in turn, controls the state of phosphorylation of numerous downstream phosphoproteins, including the dopamine and cAMP-regulated phosphoprotein of 32 kDa (DARPP-32). Caffeine, by blocking A2A receptors, reduces tonic activation of the cAMP–PKA

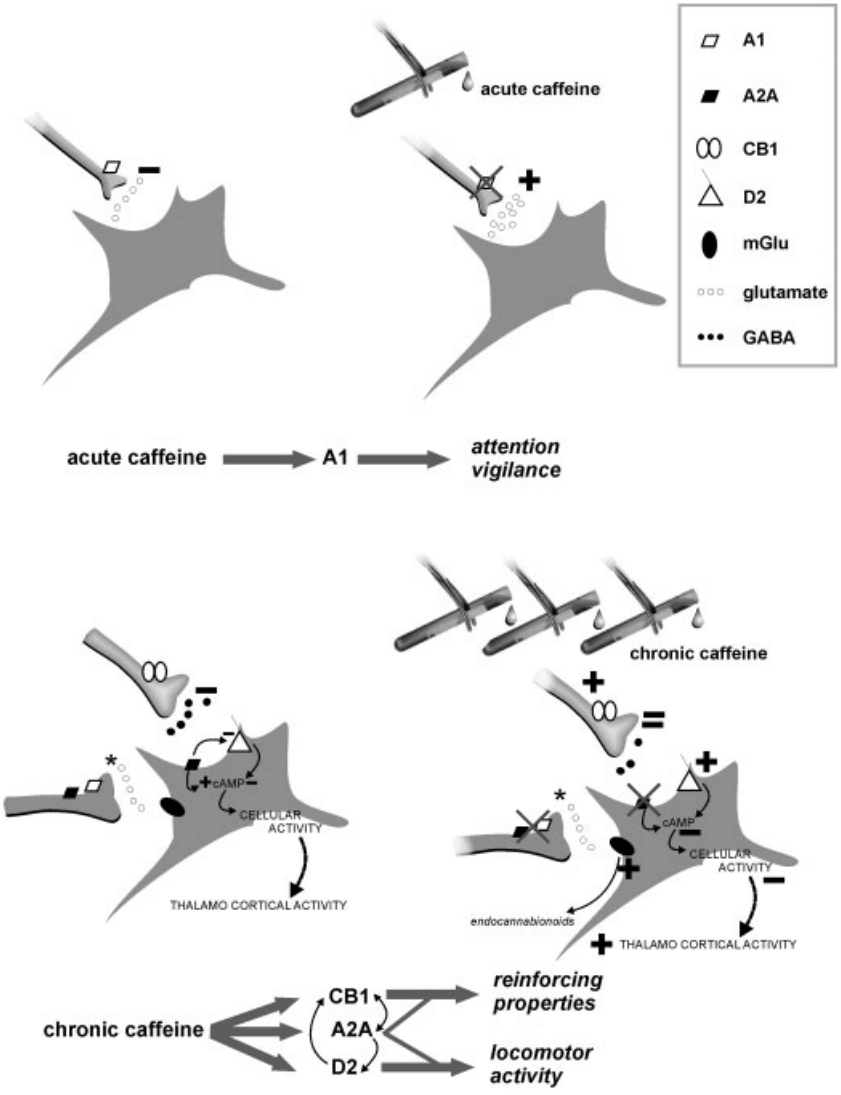

Figure 2. Schematic representation of acute and chronic caffeine effects. The figures on the left depict the physiological activity of adenosine, cannabinoid and dopamine neurotransmission. Caffeine exposure modulates these systems as shown on the right. * = Heteromers composed of isoreceptors with different affinities for adenosine can act as concentration-dependent processors that exert a fine modulation of glutamate release.

pathway, thereby affecting the activity of striatopallidal neurons. The administration of caffeine also increases the phosphorylation state of DARPP-32 at Thr75 in the mouse striatum [11, 31], and converts DARPP-32 in an inhibitor of PKA [32], further reducing phosphorylation of target proteins and amplifying its effects.

Recent evidence suggests the existence of presynaptic effects of caffeine on striatal neurotransmission. Indeed, adenosine A1–A2A receptor heteromers have been described at striatal glutamatergic nerve terminals, where they control glutamate transmission. Thus, caffeine-mediated blockade of adenosine receptors results in increased glutamate release, which activates, in turn, metabotropic mGlu5 receptors and promotes endocannabinoid release [33]. Heteromers composed of isoreceptors with different affinities for their endogenous ligands can act as concentration-dependent processors that exert a fine modulation of neurotransmission. Caffeine, regulating this fine-tuned modulation of glutamate release by adenosine, can affect the activation of output striatal neurons [33] (Fig. 2).

Besides the interaction with adenosine neurotransmission, caffeine has been recently showed to induce striatal synaptic adaptations. We have found, by means of neurophysiological recordings from single neurons, a rearrangement of cannabinoid CB1 receptor-mediated control of synaptic transmission in the striatum of mice chronically exposed to caffeine [15]. In this brain area, CB1 receptors are preferentially located on GABAergic nerve terminals [34]. Likely through A2A receptors, chronic but not acute caffeine administration sensitized GABAergic interneurons to the presynaptic effect of CB1 stimulation by HU210, but it was unable to affect CB1-mediated modulation of glutamatergic transmission. In fact, the sensitivity of glutamate synapses to CB1 receptor stimulation was unaltered in mice drinking caffeine, indicating the existence of differential regulation mechanisms of distinct cannabinoid receptors in

the striatum [15] (Fig. 3). The caffeine-induced adaptation of the endocannabinoid system was however reversible, since it declined 15 days after drug withdrawal, and was totally reversed after 1 month [15]. Notably, a similar effect on striatal cannabinoid system has also been reported after cocaine [17], suggesting that changes in the sensitivity of striatal cannabinoid receptors, common to different psychoactive drugs, could underlie the reinforcing properties of caffeine.

Even in the absence of detectable effects on cannabinoid CB1-mediated control of GABA synapses, we have found that short exposure to caffeine (1 day) was able to rescue the sensitivity of GABA synapses to CB1 receptor stimulation in mice exposed to chronic stress, a condition that conversely causes a dramatic downregulation of CB1 receptors [15, 35] (Fig. 4).

The interference of caffeine with adenosine-induced modulation of dopamine transmission might contribute to explain the sensitization of CB1 receptors induced by this psychoactive compound [30]. In this respect, the stimulation of D2 receptors has been shown to activate the endocannabinoid system and to upregulate the expression of CB1 receptors [36, 37].

Structural and functional interaction between cannabinoid and adenosine receptors has been investigated [38]. It has been demonstrated that A2A receptors could exert a permissive role on CB1 activity, since the A2A activation seems to be required for CB1 function in the striatum [39]. This assumption is also supported by molecular data showing that CB1 agonists can increase DARPP32 phosphorylation through the activation of A2A receptors [38, 40].

Caffeine-induced alteration of cannabinoid transmission may have relevant synaptic consequences during the physiological activity of the striatum, since chronic caffeine has been shown to enhance the sensitivity of GABAergic synapses not only to the synthetic cannabinoid CB1 receptor agonist, but also to endocannabinoids mobilized in response to the stimulation of metabotropic glutamate receptors [15, 39].

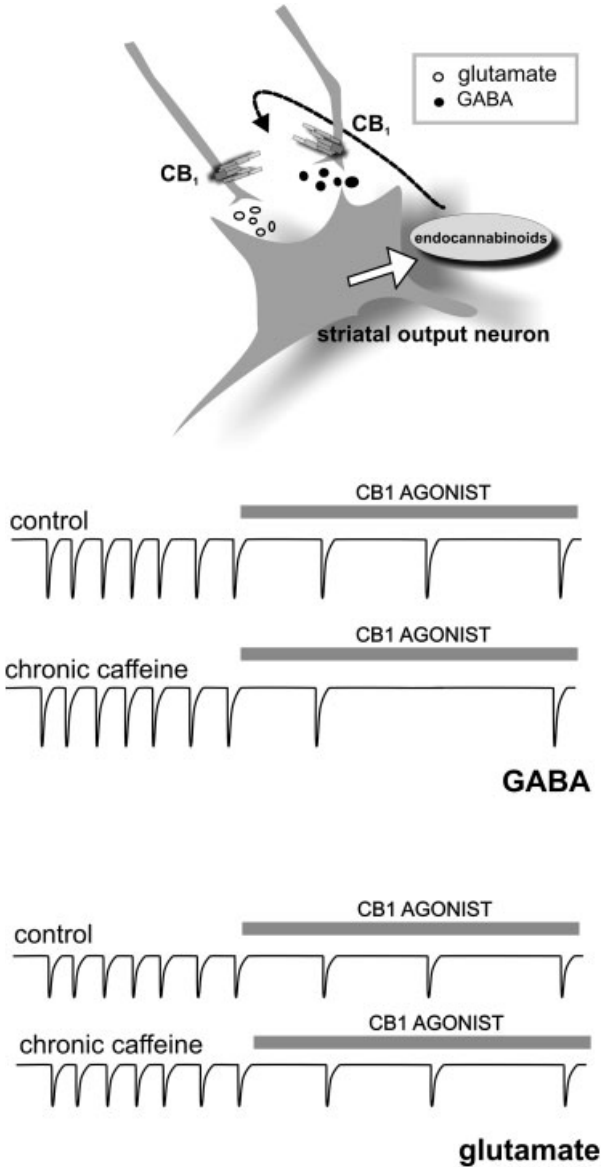

Figure 3. Scheme of the functional effects of chronic caffeine consumption on striatal endocannabinoid transmission. The endocannabinoids act as retrograde transmitters to limit GABA and glutamate release through the stimulation of presynaptic CB1 receptors. The drawings on the bottom part of the figure represent schematically the CB1-mediated inhibition of spontaneous GABAergic inhibitory postsynaptic currents (IPSCs) and of spontaneous glutamate-mediated excitatory postsynaptic currents (EPSCs), typically observed during whole-cell patch-clamp recordings of striatal neurons in control mice and after caffeine exposure. Downward deflections represent single IPSCs or EPSCs. In the original studies, GABAergic IPSCs were recorded from single neurons in the presence of pharmacological antagonists of both NMDA and non-NMDA glutamate receptors, while EPSCs were recorded in the presence of bicuculline, to block GABAA receptors (Adapted from [15] and [35]).

4 Behavioral effects

The striatum plays a key role in the central effects of caffeine [2, 11]. The psychomotor stimulant effect of caffeine is exerted, as mentioned above, by modulating the excitability of striatal medium spiny neurons through dopamine-dependent, as well as dopamine-independent mechanisms [41, 42].

Caffeine is able to enhance motor activity in experimental animals [3, 25] through its ability to affect neurotransmission within the basal ganglia [1], and to delay fatigue during exercise [43]. Typically, caffeine produces a biphasic effect on locomotor activity, since low doses increase and high doses decrease it [44, 45]. Furthermore, the caffeine-dependent stimulation of motor activity has been studied in

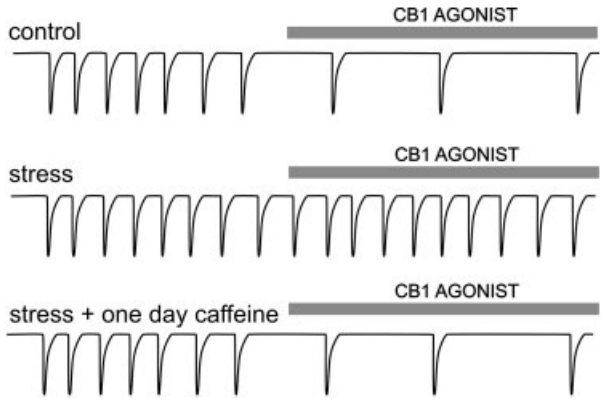

Figure 4. Example drawing of the CB1-mediated inhibition of GABAergic currents (downward deflections) observed in striatal neurons. This inhibition is present in control condition, it is abolished after stress exposure, and it is rescued by caffeine consumption. To induce psychosocial stress, C57B6 7/8-week-old mice were subjected to daily bouts for 10 min with an aggressive CD1 resident mouse, followed by 3 h protected sensory contact with their aggressor. This stress procedure causes anxious behavior in mice (Adapted from [15] and [35]).

neurological conditions characterized by low activation of thalamo-cortical projection neurons and consequent reduction of motor activity, such as Parkinson's disease. Caffeine as well as specific A2A receptor antagonists has also been shown to increase motor activity and to attenuate dopaminergic neurotoxicity in an animal model of Parkinson's disease [46].

Recently, caffeine has also been shown to induce place conditioning, to promote self-administration, and to induce psychomotor sensitization, thus mimicking the effects of psychostimulants such as cocaine [1, 3, 47, 48]. In line with this, cannabinoid receptors and DARPP-32 pathway are both modulated by caffeine exposure as well as by other psychostimulant drugs [2, 15, 17, 18].

The described cocaine- and caffeine-induced enhancement of striatal CB1 receptor sensitivity might be one of the possible mechanisms on the basis of the reinforcing properties of both psychoactive compounds, since complex and only partially overlapping adaptations in distinct neuronal circuits are likely to occur during exposure to cocaine or caffeine. However, according to the idea that similar neurobiological changes occur in response to caffeine and other psychostimulants, it has been reported that acute caffeine reinstates cocaine-seeking behavior following extinction of cocaine self-administration [49], produces cross-sensitization to nicotine [50], and favours morphine dependence [51]. Moreover, caffeine consumption has been described to increase under stress conditions, and to attenuate the psychoemotional consequences of stress [52–54]. The adaptation of striatal cannabinoid receptors induced by caffeine consumption can contribute to explain the efficacy against stress of this largely self-administered compound, because stress causes a dramatic down-regulation of CB1 receptor function [15, 35].

5 Concluding remarks

Caffeine is the most widely consumed psychoactive substance in the world. Its central effects are mainly exerted by modulating the state of excitability of striatal medium spiny neurons, where A2A receptors are abundantly expressed, and influencing other receptor systems such as dopamine, glutamate mGlu5, and cannabinoid CB1 receptors. Recent data support the hypothesis that the reinforcing properties of caffeine depend on the interaction between A2A and CB1 receptors, or also on the activation of the mGlu5 receptors, in both cases resulting in an altered CB1 receptor activity. It is also possible, however, that not only A2A but also A1 receptors play a role in the reinforcing effects of chronic caffeine.

The blockade of adenosine neurotransmission by caffeine could be considered for therapeutic implications in neurological diseases characterized by reduction of motor activity, such as Parkinson's disease. Furthermore, the modulation of the endocannabinoid system by this compound might be a valuable option to treat stress-associated neuropsychiatric conditions.

As a final consideration, it is also important to stress the concept that caffeine effects in humans are likely more complex than those described in the animal studies here resumed. Further evidence is thus necessary before considering caffeine as a valuable therapeutic option in human diseases.

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