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REVIEW

Mechanisms of the psychostimulant effects of caffeine: implications for substance use disorders

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Abstract
Background The psychostimulant properties of caffeine are reviewed and compared with those of prototypical psychostimulants able to cause substance use disorders (SUD). Caffeine produces psychomotor-activating, reinforcing, and arousing effects, which depend on its ability to disinhibit the brake that endogenous adenosine imposes on the ascending dopamine and arousal systems.
Objectives A model that considers the striatal adenosine A_{2A}-dopamine D_2 receptor heteromer as a key modulator of dopamine-dependent striatal functions (reward-oriented behavior and learning of stimulus-reward and reward-response associations) is introduced, which should explain most of the psychomotor and reinforcing effects of caffeine.
Highlights The model can explain the caffeine-induced rotational behavior in rats with unilateral striatal dopamine denervation and the ability of caffeine to reverse the adipsic-aphagic syndrome in dopamine-deficient rodents. The model can also explain the weaker reinforcing effects and low abuse liability of caffeine, compared with prototypical psychostimulants. Finally, the model can explain the actual major societal dangers of caffeine: the ability of caffeine to potentiate the addictive and toxic effects of drugs of abuse, with the particularly alarming associations of caffeine (as adulterant) with cocaine, amphetamine derivatives, synthetic cathinones, and energy drinks with alcohol, and the higher sensitivity of children and adolescents to the psychostimulant effects of caffeine and its potential to increase vulnerability to SUD.
Conclusions The striatal A_{2A}-D_2 receptor heteromer constitutes an unequivocal main pharmacological target of caffeine and provides the main mechanisms by which caffeine potentiates the acute and long-term effects of prototypical psychostimulants.

Keywords Caffeine · Psychostimulants · Adenosine · Dopamine · Receptor heteromer · Drug abuse · Alcohol

Caffeine, the most consumed psychoactive drug in the world

Caffeine is the most consumed psychoactive drug in the world. In the USA, 87 % of children and adults regularly consume foods and beverages containing caffeine (Frary et al. 2005). As discussed in the present review, its extraordinary frequent and widespread use depends on its unique psychostimulant properties. It has long been recognized that caffeine is a psychostimulant with milder pharmacological effects than prototypical psychostimulants, like amphetamine and cocaine. The terms "psychostimulant" or "psychomotor stimulant" are to be distinguished from "general central nervous system stimulant" such as strychnine and pentylenetetrazol or picrotoxin, antagonists of the inhibitory neurotransmitter receptors for glycine and GABA, respectively (Huang et al. 2001; Dutertre et al. 2012). Psychomotor activation is a major pharmacological effect of psychostimulants, while general central nervous system stimulants fail to increase psychomotor activity at doses below those that produce convulsions. As elaborated in the following chapter, psychomotor activation implies a behavioral response to specific environmental stimuli, more specifically reinforcing stimuli. And, in addition

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to inducing psychomotor activation, psychostimulants have reinforcing and arousing effects. It is one of the tenets of the present review that these three pharmacological effects contribute to caffeine use.

Psychostimulants elicit their psychomotor-activating and reinforcing effects by their ability to increase central dopamine neurotransmission (see next chapter). Since caffeine is a non-selective competitive antagonist for adenosine A_1 and A_{2A} receptors (Fredholm et al. 1999), long-standing challenges have been to determine the ability of adenosine to modulate central dopamine neurotransmission and the mechanisms by which blockade of adenosine neurotransmission leads to the psychostimulant effects of caffeine. A large number of experimental data indicate that heteromers of A_{2A} and dopamine D_2 receptors localized in a specific striatal neuronal population are largely responsible for the integration of central adenosine and dopamine neurotransmission that is involved in the psychomotor and reinforcing effects of caffeine. Another tenet of the present review is that the functional and pharmacological properties of striatal A_{2A}-D_2 receptor heteromers can explain a large component of what should be considered as the major societal dangers of caffeine, particularly the ability of caffeine to potentiate the addictive and toxic effects of drugs of abuse and the special sensitivity of children and adolescents to the psychostimulant effects of caffeine with its potential to increase vulnerability to substance use disorders (SUD).

Wise and Bozarth's psychomotor stimulant theory of addiction and Ungerstedt's Ph.D. thesis

In their most influential "Psychomotor Stimulant Theory of Addiction," Wise and Bozarth (1987) postulated that psychomotor activation and reinforcing effects constitute different aspects of the same underlying mechanism: an increase in central dopamine neurotransmission. In their seminal paper, Wise and Bozarth (1987) eloquently extended the theory of Glickman and Schiff (1967), which holds that all positive reinforcers should elicit approach to localized stimuli or some generalized form of forward locomotion, to the case of addictive drugs.

Wise and Bozarth first elaborated on the distinction between "psychomotor" and simply "motor" responses. The two most commonly identified psychostimulant-induced psychomotor responses in the experimental animal are "locomotion" and "stereotypy." It is generally but faultily accepted that forward locomotion and stereotypy induced by psychostimulants are motor responses that result from increased dopamine transmission in the ventral striatum (nucleus accumbens) and the dorsal striatum (caudate-putamen), respectively. Both types of responses have a characteristic dependence on external (environmental or somatic) stimuli, and what psychostimulants do is to produce an increased responsiveness to those stimuli (Miller and Beninger 1991). The opposite is seen with genetic or pharmacological blockade of dopamine (Wise and Bozarth 1987; Szczypka et al. 2001) or with selective lesions of the ascending dopamine pathways or targeted dopamine denervation of striatal areas (Ljungberg and Ungerstedt 1976; Marshall et al. 1980; Miyashita et al. 1995), where the animals develop sensory neglect, inattention to relevant stimuli, rather than a simple motoric or sensory impairment.

In 1971, Urban Ungerstedt published one of the most influential Ph.D. theses ever written in the field of neuroscience (Ungerstedt 1971a, b, c, d). He described in detail the mapping of the monoaminergic systems and demonstrated the functional effects of unilateral or bilateral selective lesions (with 6-hydroxydopamine, 6-OHDA) of the ascending dopamine systems. With a device he invented to quantify rotational behavior in rats with unilateral 6-OHDA lesions, the rotometer, he established what was later known as "Ungerstedt's method," which became a very useful model to screen drugs with potential antiparkinsonian activity. The most striking finding was the qualitative difference between an indirect dopamine receptor agonist like amphetamine, which induces large increases of extracellular dopamine, and a direct dopamine receptor agonist like apomorphine, which directly activates dopamine receptors. Amphetamine and apomorphine produced completely opposite behaviors, with strong rotational behavior ipsilateral and contralateral to the lesioned side, respectively (Ungerstedt 1971b, c). Finally, he found that a bilateral lesion of the ascending dopamine systems reproduces the previously described "lateral hypothalamic syndrome," characterized by aphagia and adipsia (Teitelbaum and Epstein 1962). The symptoms were the same as those reported from more recent studies in genetic dopamine-deficient animals (Ungerstedt 1971d; Palmiter 2008). In both cases, the animals have to be tube-fed or administered direct dopamine receptor agonists to reverse their symptoms in order to survive, and in both cases, they showed pronounced hypokinesia (Ungerstedt 1971d; Palmiter 2008).

Ungerstedt wrote: "…the role of the striatum is in all probability not one of regulating eating and drinking specifically. When considering the curious hypokinesia, lack of exploratory behavior and difficulty to initiate activity that occurs after selective lesions of the nigro-striatal dopamine system it is more probable the dopamine system and the striatum control a general arousal or drive level that is necessary for performing a number of activities, where eating and drinking deficits are noticed only because they are easily measured by the observer and disastrous to the animal" (Ungerstedt 1971d). Subsequent studies showed that impaired orientation to sensory stimuli constitutes a predominant deficit after lesioning the ascending dopamine systems, particularly the nigro-striatal system or its striatal target area (Ljungberg and

Ungerstedt 1976; Marshall et al. 1980). In fact, Marshall et al. (1971) had shown that unilateral lateral hypothalamic lesions in rats produce deficits in orientation to contralateral visual, olfactory, whisker-touch, and somatosensory stimuli. It follows that turning behavior induced by dopamine agonists in unilateral 6-OHDA-lesioned rats is not the result of an asymmetrical dopamine activation of locomotor mechanisms but that of an asymmetrical attention to relevant stimuli (Miller and Beninger 1991). Sensory neglect contralateral to the lesioned side makes the animal turning spontaneously or when disturbed (e.g., by pinching its tail) towards the lesioned side (Ungerstedt 1971b). Upon administration with prototypical psychostimulants, such as amphetamine or cocaine, the predominant activation of dopamine receptors in the non-denervated striatum induced by a large dopamine release significantly increases the interest of the animal for stimuli coming from the lesioned side, leading to strong ipsilateral turning. On the other hand, low doses of direct dopamine receptor agonists lead to a predominant activation in the striatum ipsilateral to the lesion, which is dependent on a dopamine denervation-induced upregulation (increased density or functional response) of dopamine D_1 and D_2 receptors (Creese et al. 1977; Neve et al. 1984; Gerfen et al. 2002). This increases the interest of the animal for stimuli coming from the non-lesioned side, to contralateral turning (Ungerstedt 1971b, c; Ljungberg and Ungerstedt 1976). Pharmacologically, the up-regulation of dopamine receptors in the denervated compared to the ipsilateral striatum is demonstrated by the substantial increase in the potency of direct dopamine receptor agonists at inducing contralateral turning and by the elicitation of the same qualitative rotational behavior when intracranially administered in the striatum ipsilateral to the 6-OHDA lesion (Herrera-Marschitz et al. 1985). In summary, direct and indirect dopamine receptor agonists reproduce or potentiate, respectively, the effect of endogenous dopamine on increasing responsiveness to salient stimuli with orienting and approaching behavior.

After ascertaining the concept of psychomotor activity, Wise and Bozarth (1987) emphasized the evidence of psychomotor-activating effects for all known addictive drugs, including those generally considered as central nervous system depressants, such as opiates, alcohol, barbiturates, and cannabinoids. The next move was to regard positive reinforcement as a main mechanism involved in drug dependence, and then, they postulated that psychomotor-activating and reinforcing effects of all addictive drugs share a common mechanism, activation of ascending dopamine systems. The crux of the theory was that the reinforcing effects of drugs, and thus their addiction liability, could be predicted from their ability to induce psychomotor activation (Wise and Bozarth 1987). A large amount of experimental data has accumulated since the formulation of the psychomotor stimulant theory of addiction about the function of dopamine and the ascending dopamine system. The work by Wolfgang Schultz has been of particular significance. He demonstrated that mesencephalic dopamine cells are particularly involved in the processing of a particular kind of salient stimuli: rewarding stimuli and reward-associated stimuli. Basically, two different temporal operating modes of dopamine neuronal function have been described: first, a fast, millisecond-scale, phasic response, which codes for a reward prediction error (Schultz 2002), which therefore provides a rapid response to reward-related signals and can significantly contribute to the role of dopamine in reinforcement and, second, a prolonged, minute-scale, tonic dopamine modulation (Schultz 2002), which provides signals of proximity and value of distant rewards (Howe et al. 2013) and therefore can significantly contribute to the role of dopamine in reward-oriented behaviors.

Dopamine is then particularly involved with increasing responsiveness to rewarding stimuli, with orienting and approaching responses to those stimuli, with reward-oriented behavior. But, concomitantly, dopamine is directly involved in reinforcement, in the learning ("stamping-in") of stimulus-reward and reward-response associations that follows the receipt of reward (Wise 2004). The reinforcement of stimulus-reward associations establishes signals that guide and orient to rewards (discriminative stimulus) or that become rewards themselves (conditioned rewarding stimulus). The stamping-in of reward-response associations promotes the learning of the optimal sequential response, the action skill that leads to the reward. The insightful model of basal ganglia function developed by Kim and Hikosaka (2015), based on their elegant experiments on gaze orienting and learning of sequential motor responses in non-human primates, highlights the simultaneous processing of reward-oriented behaviors and reinforcement by all striatal areas. The model also implies that, in support of the psychomotor stimulant theory of addiction, all dopamine-dependent functions (reward-oriented behavior and learning of stimulus-reward and reward-response associations) are simultaneously processed in all striatal areas. In relation to reinforcement, rostral areas are predominantly involved in an initial, more controlled, "volitional" (contingent on the outcome), accurate, and more labile learning, while caudal areas are involved in a slower and more "automatic" (non-contingent on the outcome) and long-lasting learning (Kim and Hikosaka 2015). The same functional dichotomy has been demonstrated in the rodent striatum, but with a medial-lateral distribution, with medial and lateral striatum being preferentially involved with outcome-dependent and independent learning, respectively (Yin 2006). Both in primates and rodents, this functional striatal heterogeneity fits very nicely with a differential cortical glutamatergic and mesencephalic dopamine innervation (Voorn et al. 2004; Ikemoto 2010; Kim and Hikosaka 2015). In summary, our actual knowledge about the functions of dopamine in the striatum underscores this subcortical structure as being particularly

involved in the psychomotor-activating and reinforcing effects of psychostimulants.

However, an increasing number of experimental data also indicate that mesencephalic dopamine cells also process aversive stimuli (for recent review, see Holly and Miczek 2016). Electrophysiological experiments have found evidence for the existence of two separated populations of dopamine neurons that respond differently to aversive stimuli. Most dopamine cells respond by decreasing their activity, and these are cells that also increase their firing upon presentation of rewarding stimuli or with the termination of an aversive stimulus (Brooks and Berns 2013; Abraham et al. 2014). The other subpopulation increases its activity upon presentation of an aversive stimulus, and it seems to be specifically localized in the most medial and posterior part of the ventral tegmental area (pmVTA; Brooks and Berns 2013; Abraham et al. 2014; Lammel et al. 2014). In fact, this area projects to a specific striatal area, also the posteriomedial part of the shell of the nucleus accumbens (pmNAc shell; Vertes 2004; Quiroz et al. 2016), specifically involved in threat-related behaviors (Richard et al. 2013). The infralimbic cortex innervates both pmVTA and pmNAc shell as well as the amygdala, and this circuit plays a key role in "fear" extinction, in the suppression of threat conditioning (Vidal-Gonzalez et al. 2006; Knapska et al. 2012). Importantly, according to Moscarello and LeDoux (2013), active avoidance learning, with the elicitation of a behavioral response that avoids the interaction with the aversive stimulus, requires the suppression of threat conditioning. Then, dopamine is associated not only with positive but also with negative reinforcement. In summary, *dopamine promotes approach by directly increasing the responsiveness to reward-related stimuli*, *but also indirectly by decreasing the withdrawal reaction from previously conditioned aversive stimuli*. This indirect mechanism could then be involved in the insensitivity to the aversive stimuli in subjects with SUD (McCutcheon et al. 2012). In fact, in some experimental models of SUD, the animal continues to respond to the drug even if they must endure a foot shock that otherwise would be aversive (Deroche-Gamonet et al. 2004).

Psychomotor-activating effects of caffeine: the striatal adenosine A_{2A}-dopamine D_2 receptor heteromer

Unexpected findings about caffeine were observed when Ungerstedt's model became established as a reliable method to elucidate the direct or indirect characteristics of a putative dopamine receptor agonist. Caffeine (and theophylline) potentiated the contralateral turning behavior (in rats with a unilateral 6-OHDA lesion of the ascending dopamine system) induced by direct dopamine receptor agonists and elicited contralateral turning when administered on its own (Fuxe and Ungerstedt 1974). Since it was soon realized that caffeine did not bind to dopamine receptors, a series of studies followed trying to find the dopamine receptor agonist-like mechanism involved. The intensity of contralateral turning induced by caffeine significantly correlated with that induced by the direct non-selective dopamine receptor agonist apomorphine and was counteracted by dopamine receptor antagonists (Herrera-Marschitz et al. 1988; Casas et al. 1989; Garrett and Holtzman 1995a). More specifically, D_2 but not D_1 receptor antagonists counteracted caffeine-induced turning behavior (Garrett and Holtzman 1995a). Differently from apomorphine, these psychomotor-activating effects of caffeine seemed to be totally dependent on the upregulation of dopamine receptors caused by the striatal dopamine denervation. Thus, apomorphine but not caffeine produced ipsilateral rotational behavior in rats with unilateral striatal kainic acid lesions (Herrera-Marschitz et al. 1988). The dependence on dopamine receptor upregulation was also demonstrated by the ability of caffeine to counteract dopamine depletion-induced psychomotor depression in reserpinized mice. Systemic administration of reserpine produces catecholamine depletion. This translates into complete akinesia that can be reversed by direct dopamine receptor agonists, either after short- or long-term reserpinization (about 4 or 24 h after reserpine administration, respectively; Starr et al. 1987; Ferré et al. 1991a, b; Giménez-Llort et al. 1995). The same as with dopamine denervation, long-term reserpinization is associated with upregulation of dopamine receptors with increased sensitivity to the psychomotor-activating effects of direct dopamine receptor agonists (Burt et al. 1977). Caffeine and related xanthines produce significant locomotor activity in long- but not short-term reserpinized animals (Ferré et al. 1991b; Giménez-Llort et al. 1995; Shiozaki et al. 1999).

Previous sensitization with direct dopamine receptor agonists was found to be essential in order to observe a contralateral behavior induced by caffeine (Fenu and Morelli 1998). Thus, classically, apomorphine was always repeatedly administered to demonstrate the existence of a significant unilateral 6-OHDA lesion, leading to a progressive and significant increase in apomorphine-induced contralateral turning (Ungerstedt 1971c; Herrera-Marschitz et al. 1985; Pollack et al. 1997; Fenu and Morelli 1998). Hence, unless previous sensitization of a direct dopamine receptor has been established, caffeine behaves as an indirect dopamine receptor agonist and tends to produce ipsilateral turning (Fenu and Morelli 1998; Cauli et al. 2003). The other way around, repeated but intermittent (non-daily) systemic caffeine administration, a schedule that is not associated with tolerance to its psychostimulant effects, sensitizes the rat to the contralateral and ipsilateral turning induced by direct and indirect dopamine receptor agonists, respectively (Cauli et al. 2003, 2005; Pollack et al. 2010).

Sensitization to direct or indirect dopamine receptor agonists in naïve, non-denervated animals is a well-recognized phenomenon that consists of a progressive increase in their psychomotor-activating effects that are strongly dependent on the environment in which the drug is administered. The phenomenon extends to all addictive drugs, with their dependence on dopaminergic mechanisms, and it has been suggested to be involved in the development of drug addiction (Kalivas and Stewart 1991; Robinson et al. 1998). Again, non-tolerance-associated continuous caffeine exposure (low caffeine concentration in the drinking water) or repeated intermittent caffeine administration induces environment-dependent sensitization to its psychomotor effects and cross-sensitization to direct and indirect dopamine receptor agonists, such as amphetamine (Gasior et al. 2000; Cauli and Morelli 2002; Simola et al. 2006; Zancheta et al. 2012). On the other hand, strong tolerance develops to the psychostimulant effects of caffeine (including turning behavior in rats with a unilateral 6-OHDA lesion) upon continuous caffeine exposure (high caffeine concentration in the drinking water) or repeated daily (systemic) caffeine administration (Holtzman and Finn 1988; Garrett and Holtzman 1995b; Howell and Landrum 1997; Karcz-Kubicha et al. 2003; Quarta et al. 2004a). Nevertheless, both sensitization and tolerance to the psychomotor effects of caffeine are independent processes and therefore dependent on different mechanisms. In fact, a washout period of several days after a tolerance-associated continuous or repeated caffeine treatment discloses an apparently latent caffeine sensitization (Hsu et al. 2009, 2010). As mentioned below, caffeine sensitization is A_{2A} receptor mediated and preferentially involves long-lasting postsynaptic changes, including increased phosphorylation of the cAMP-regulated phosphoprotein of molecular weight 32 kDA (DARPP-32; Hsu et al. 2009). On the other hand, tolerance depends mostly on presynaptic A_1 receptor-mediated mechanisms (see below). Altogether, caffeine demonstrates unique pharmacological properties as compared with other psychostimulants: It induces psychomotor activation which qualitatively resembles that of direct or indirect dopamine receptor agonists depending on the experimental conditions; *dopamine denervation and previous sensitization with direct dopamine receptor agonists discloses and intensifies the apparent direct dopamine receptor agonistic properties of caffeine*.

The enigmatic psychomotor-activating effects of caffeine provided one of the main initial findings that would lead to the field of G protein-coupled receptor heteromers (Ferré et al. 2009, 2014). More specifically, it led to the discovery of adenosine-dopamine receptor heteromers (Ferré et al. 1997, 2007). And even more specifically, it led to the establishment of A_{2A}-D_2 receptor heteromers as mainly responsible for the psychostimulant effects of caffeine (Ferré et al. 2015). The first evidence came from experiments in short-term reserpinized mice showing differences in the counteracting effects of adenosine receptor agonists on D_2 receptor agonist-induced locomotor activation. The order of potency of the adenosine receptor agonists indicated a selective antagonistic interaction between A_{2A} and D_2 receptors (Ferré et al. 1991a). Furthermore, the effects of A_{2A} receptor activation were dose-dependently counteracted by caffeine and related methylxanthines (Ferré et al. 1991b).

With the availability of selective A_{2A} receptor ligands, a large number of experiments demonstrated that A_{2A} receptor agonists and antagonists induce the same qualitative psychomotor depressant and activating effects as D_2 receptor antagonists and agonists, respectively (Ferré et al. 1991c; Kanda et al. 1994; Rimondini et al. 1997; Shiozaki et al. 1999; Randall et al. 2011; Nunes et al. 2013), that A_{2A} receptor agonists and antagonists selectively counteract and potentiate the psychomotor-activating effects of D_2 receptor agonists, respectively (Popoli et al. 1996; Rimondini et al. 1998; Strömberg et al. 2000; Ferré et al. 2001), but also that selective A_{2A}, but not A_1, receptor antagonists counteract the psychomotor depressant effects of reserpine and D_2 receptor antagonists (Kanda et al. 1994; Shiozaki et al. 1999; Pardo et al. 2012; Nunes et al. 2013; Minor and Hanff 2015). Initial studies dealt mostly with locomotor activity recording, but more recent studies about the psychomotor-activating effects of caffeine also dealt with measures of specific reward-oriented behavior, with caffeine and A_{2A} receptor antagonists increasing the responsiveness to specific rewarding stimuli, such as those associated with regular food (Randall et al. 2011; Nunes et al. 2013), sucrose solutions (Brianna Sheppard et al. 2012), and those eliciting maternal behavior (Pereira et al. 2011) and intracranial self-stimulation (Lazenka et al. 2015). Lastly, A_{2A} but not A_1 receptor antagonists induce sensitization to their psychomotor-activating effects and cross-sensitization to caffeine (Hsu et al. 2009, 2010).

A_{2A} and D_2 receptors were found particularly expressed in the striatum and co-localized in the same neuron, the GABAergic striato-pallidal neuron (Schiffmann et al. 1991; Ferré et al. 1991). Together with the GABAergic striato-nigral neuron, they constitute more than 90 percent of the entire neuronal population. We have now a large amount of experimental evidence for the existence of a predominant striatal population of both A_{2A} and D_2 receptors forming functionally and pharmacologically significant heteromers that modulate the function of the GABAergic striato-pallidal neurons (Ferré et al. 1993, 2015; Azdad et al. 2009; Bonaventura et al. 2015). This predominant population of specific subtypes of adenosine and dopamine receptors localized in one of the two predominant populations of striatal neurons provides a frame for the apparent preferential role of A_{2A} and D_2 receptors in the psychostimulant effects of caffeine. Recent studies suggest that A_{2A}-D_2 receptor heteromers constitute a heterotetrameric structure with A_{2A} and D_2 receptor homodimers coupled to their cognate Gs/olf and Gi/o protein, respectively (Bonaventura et al. 2015; Ferré 2015). The heterotetrameric structure allows multiple

simultaneous and reciprocal interactions between adenosine and dopamine and exogenous A_{2A} and D_2 receptor ligands (Navarro et al. 2014; Bonaventura et al. 2015; Ferré et al. 2015). Two most salient interactions are the ability of adenosine or exogenous A_{2A} receptor ligands to decrease the affinity and intrinsic efficacy of dopamine or exogenous D_2 receptor ligands (allosteric A_{2A}-D_2 interaction) and the ability of D_2 receptor agonist-mediated and Gi/o protein-dependent counteraction of A_{2A} receptor agonist-mediated and Gs/olf-dependent activation of adenylyl-cyclase (adenylyl-cyclase A_{2A}-D_2 interaction). In fact, it can be postulated that the canonical Gs-Gi interaction at the adenylyl-cyclase level depends on heteromerization of Gs- and Gi-coupled homodimers (Guitart et al. 2014; Navarro et al. 2014; Ferré 2015). One more recently discovered interaction is a negative allosteric modulation between an orthosteric A_{2A} receptor agonist and an antagonist binding simultaneously to the A_{2A} receptor homodimer within the A_{2A}-D_2 receptor heterotetramer (Bonaventura et al. 2015). Negative allosterism between caffeine and endogenous adenosine, more than competitive antagonism, seems to be mostly involved with the psychomotor effects of caffeine (Bonaventura et al. 2015). The A_{2A}-D_2 receptor heteromer acts as an integrative device that allows very elaborated interactions between adenosine and dopamine controlling the function of the GABAergic striato-pallidal neuron: preferential A_{2A} versus D_2 receptor activation leads to an increased neuronal activity by activating adenylyl-cyclase and by allosterically counteracting D_2 receptor signaling; preferential D_2 versus A_{2A} receptor activation leads to a decreased neuronal activity by G protein-dependent and independent mechanisms and by counteracting A_{2A} receptor-mediated activation of adenylyl-cyclase (Navarro et al. 2014; Bonaventura et al. 2015; Ferré et al. 2015). Increases or decreases in the activity of the GABAergic striato-pallidal neuron leads to the opposite, decreases and increases in psychomotor activity, respectively. Thus, a pathogenic hallmark of akinesia in Parkinson's disease is a pronounced hyperactivity of the GABAergic striato-pallidal neuron. This is in fact the rationale for our originally suggested (Ferré et al. 1992) and recently implemented use of A_{2A} receptor antagonists in this disease (Müller and Ferré 2007; Morelli et al. 2009; Armentero et al. 2011).

Under resting physiological conditions, there is a tonic activation of A_{2A} and D_2 receptors by the endogenous neurotransmitters with a final integration resulting in predominant A_{2A} versus D_2 receptor signaling and a predominant allosteric A_{2A}-D_2 receptor interaction (Fig. 1a), leading to low psychomotor activity. In the presence of rewarding-related stimuli, striatal dopamine release leads to a predominant D_2 versus A_{2A} receptor signaling, now with a predominant adenylyl-cyclase A_{2A}-D_2 receptor interaction (Fig. 1b), leading to psychomotor activation. Maybe not surprisingly, if we consider A_{2A} and D_2 receptors as one functional receptor unit, dopamine depletion by reserpine, 6-OHDA lesion, or genetic engineering leads to a prominent upregulation (increased density

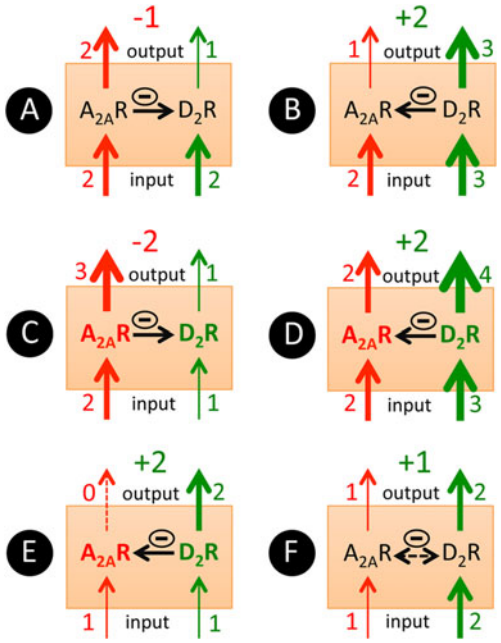

Fig. 1 Model of the striatal A_{2A}-D_2 receptor heteromer as a main mechanism for the psychomotor and reinforcing effects of psychostimulants. The relative thickness (and *close number*) of the *red* and *green input arrows* represents the degree of activation of the A_{2A} receptor ($A_{2A}R$) and the D_2 receptor (D_2R) that depends on the concentration of the corresponding neurotransmitter or exogenous ligands. *Bold* and *colored* $A_{2A}R$ and D_2R represent dopamine denervation-induced upregulated receptors. The thickness (and *close number*) of the *red* and *green output arrows* represents the intensity of A_{2A} and D_2 receptor signaling, respectively, which depends on the input signal for each receptor, on the sensitivity of each receptor (basal or upregulated), and on the predominance of antagonistic allosteric and adenylyl-cyclase A_{2A}-D_2 receptor interactions (represented by *horizontal arrows* with a *minus enclosed sign*; in ***F***, the *broken line* with *double arrowhead* indicates weak and non-predominant interactions). Predominant psychomotor activation or depression will result when subtraction of the A_{2A} receptor signaling from the D_2 receptor signaling gives a positive (also in *green*) or negative (also in *red*) value, respectively. ***A***, Resting condition; ***B***, presence of rewarding stimulus or after administration of a direct or indirect dopamine receptor agonist without dopamine depletion; ***C***, dopamine depletion; ***D***, administration of a direct dopamine receptor agonist with dopamine depletion; ***E*** administration of caffeine or/and A_{2A} receptor antagonist with dopamine depletion; ***F***, administration of caffeine or/and A_{2A} receptor antagonist without dopamine depletion (see text)

or functional response) of both D_2 and A_{2A} receptors (Burt et al. 1977; Creese et al. 1977; Neve et al. 1984; Ferré and Fuxe 1992; Pinna et al. 2002; Bhattacharjee et al. 2011). In fact, both receptors have been found to be upregulated in patients with Parkinson's disease (Antonini et al. 1995; Ichise et al. 1999; Hurley et al. 2000; Calon et al. 2004; Varani et al. 2010). Then, the model that considers A_{2A} and D_2 receptor signaling, their interactions, and their dopamine depletion-dependent upregulation in the frame of the A_{2A}-D_2 receptor heteromer can explain the psychomotor-activating effects of caffeine. Based on experimental findings from dopamine-depleted animals, the model assumes that

adenosine plays a much more important role than previously suspected. Upregulation of D_2 receptors can compensate for the small but still functional concentration of extracellular dopamine, but upregulation of A_{2A} receptors increases the effect of endogenous adenosine and shifts the balance between A_{2A} and D_2 receptor signaling even further in favor to A_{2A}, leading to pronounced neglect of rewarding stimuli, to psychomotor depression (Fig. 1c). Under these conditions, either a D_2 receptor agonist (Fig. 1d) or caffeine or a selective A_{2A} receptor antagonist (Fig. 1e) changes the balance to a predominant D_2 receptor signaling, leading to increased responsiveness to rewarding stimuli, to psychomotor activation. Without dopamine depletion, without upregulation of A_{2A} or D_2 receptors, caffeine or a selective A_{2A} receptor antagonist produces a less-pronounced imbalance in favor of dopamine

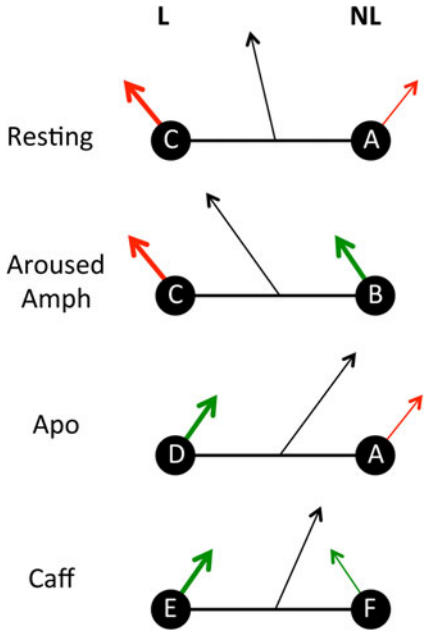

Fig. 2 Model of the striatal A_{2A}-D_2 receptor heteromer as a main mechanism for the rotational behavior in unilateral 6-OHDA-lesioned rats induced by direct and indirect dopamine receptor agonists and by caffeine. The *circles* represent striata from the dopamine-denervated, lesioned side (*L*) and from the non-lesioned side (*NL*). Each *letter* indicates the condition of the striatum as defined in Fig. 1, under resting conditions, when aroused or with amphetamine (Amph) administration, and after apomorphine (Apo) or caffeine (Caff) administration. The *output arrows* are the result of either predominant A_{2A} or D_2 receptor signaling (*red* or *green*, respectively) from each striatum. A *green arrow* implies predominant D_2 receptor signaling and increased responsiveness for rewarding stimuli in the contralateral site and therefore a trend for turning behavior contralateral to the striatum. A *red arrow* implies predominant A_{2A} receptor signaling and decreased responsiveness for rewarding stimuli in the contralateral site and therefore a trend for turning behavior ipsilateral to the striatum. The thickness of each *colored arrow* represents the relative intensity (as in Fig. 1) of the final signaling from each striatum. The *black arrow* points to the direction of the rotational behavior, ipsilateral or contralateral to *L*: either none or a trend for ipsilateral turning under resting conditions, ipsilateral turning when aroused or with Amph administration, and contralateral turning after Apo or Caff administration

by blocking less potently A_{2A} receptors, but still being able to produce an increase in psychomotor activity (Fig. 1f). As shown in Fig. 2, the model can explain the rotational behavior in rats with unilateral striatal dopamine denervation, not only the ipsilateral and contralateral turning to the lesion side induced by indirect and direct dopamine receptor agonists, respectively, but also the contralateral turning induced by caffeine (see figure legend for details). The model, which implies a significant "active" role of adenosine on the depressant psychomotor effects produced by dopamine depletion, a situation of bilateral dopamine-denervated striata (Fig. 1c), can also explain the ability of caffeine to reverse the adipsic-aphagic syndrome in bilateral 6-OHDA-lesioned rats (Casas et al. 2000) and in genetically induced dopamine-deficient mice (Kim and Palmiter 2003; Palmiter 2008) (Fig. 1e). In these mice, in fact, a selective A_{2A} but not an A_1 receptor antagonist induced feeding and locomotion (Kim and Palmiter 2003).

In summary, *the accumulated knowledge about the function of the striatal A_{2A}-D_2 receptor heteromer demonstrates that it is a main target for the psychomotor-activating effects of caffeine*. However, this is still an incomplete picture. Caffeine also increases dopamine neurotransmission by additional mechanisms related to blockade of striatal presynaptic A_1 receptors that modulate dopamine and glutamate release (Quarta et al. 2004b; Ciruela et al. 2006) and postsynaptic A_1 receptors that form heteromers with D_1 receptors in the GABAergic striato-nigral neuron (Ferré et al. 1997; Ferré 2008). A series of experiments performed in the laboratory of Steven Goldberg demonstrated the involvement of A_1 receptors in the acute psychomotor-activating (locomotor activity), discriminative-stimulus, and dopamine-releasing effects of caffeine (Solinas et al. 2002, 2005; Karcz-Kubicha et al. 2003; Quarta et al. 2004a, b; Antoniou et al. 2005; Borycz et al. 2007). Nevertheless, tolerance developed to the effects of A_1 receptor blockade upon continuous caffeine exposure in the drinking water, while its residual locomotor-activating effects depended mostly on A_{2A} receptor blockade (Karcz-Kubicha et al. 2003; Quarta et al. 2004a). In the same line of research, it was shown that upon repeated and frequent (twice daily) treatment, tolerance did not develop to the locomotor effects of an A_{2A} antagonist (Halldner et al. 2004). Importantly for the therapeutic implications for Parkinson's disease, tolerance did not develop either to the potentiating effects of A_{2A} receptor antagonists on the psychomotor-activating effects (turning behavior) of D_2 receptor agonists or L-dopa (Popoli et al. 2000; Pinna et al. 2001). The precise mechanisms for caffeine tolerance are not yet fully elucidated but involve several pharmacokinetic and pharmacodynamic variables that include increase in plasma adenosine levels (Conlay et al. 1997) and upregulation with increased density or functional response of A_1 receptors (Jacobson et al. 1996; Karcz-Kubicha et al. 2003). These seemingly compensatory changes lead to an increased adenosine tone, which is well

manifested upon withdrawal. Thus, withdrawal from chronic treatment with caffeine leads to a significant reduction of spontaneous psychomotor activity (measured as spontaneous locomotion) and a reduction of adenosine receptor agonist-induced psychomotor depression (Nikodijević et al. 1993).

A_1 receptor also plays a role in the arousing effects of caffeine, which can be dissociated from the other psychostimulant effects in terms of the underlying mechanism, since they are mostly independent of the activity of the ascending dopamine systems (reviewed in Ferré 2010). Adenosine is a main mediator of sleepiness following prolonged wakefulness, when it accumulates in the extracellular space of the basal forebrain, cortex, and hypothalamus (Porkka-Heiskanen et al. 2000; Basheer et al. 2004; McCarley 2007). This accumulation depends on ATP released from astrocytes and converted to adenosine in the extracellular space (Hines and Haydon 2014), which leads to: A_1 receptor-mediated inhibition of the cells of origin of the corticopetal basal forebrain system (Basheer et al. 2004; McCarley 2007); inhibition of corticofugal neurons from the prefrontal cortex that target the origin of pontine ascending arousal systems (Van Dort et al. 2009), also mediated by A_1 receptors; and inhibition of hypothalamic histaminergic and orexinergic ascending arousal systems, with both A_1 and A_{2A} receptors being involved (Huang et al. 2005; McCarley 2007; Szymusiak and McGinty 2008; Lazarus et al. 2011). *By disinhibiting adenosine-mediated inhibition of the ascending arousal systems, caffeine also increases the responsiveness to non-rewarding salient stimuli.*

Reinforcing effects of caffeine and the *DSM-5*

As reviewed so far, the same as prototypical psychostimulants (cocaine, amphetamine), caffeine has arousing and psychomotor-activating effects, which depend on its ability to disinhibit the brake that endogenous adenosine imposes on the ascending arousal and dopamine systems, respectively. According to the psychomotor stimulant theory of addiction, its psychomotor-activating effects predict reinforcing effects and addiction liability. In fact, acute caffeine administration induces as much or even more pronounced psychomotor activity than opiates, nicotine, THC, barbiturates or alcohol, all well-established substances with reinforcing and addictive properties. Reinforcing effects of caffeine can be demonstrated in the experimental animal and humans. However, as discussed below, both in humans and in the experimental animal, caffeine demonstrates weaker reinforcing effects as compared to prototypic psychostimulants and other common addictive substances. Nevertheless, in drug-discrimination studies in users of prototypical psychostimulants, low to intermediate doses of caffeine produce a profile of positive subjective effects similar to those of amphetamine and cocaine, while with high doses of caffeine the subjects report aversive subjective feelings of anxiety and nervousness (Garrett and Griffiths 1997).

In the experimental animal, caffeine-induced learning of stimulus-reward associations has been well documented, although there are no conclusive results about learning of reward-response associations. Thus, the experimental animal develops taste preference for flavors associated with caffeine (Brockwell et al. 1991; Fedorchak et al. 2002; Myers and Izbicki 2006) but maintains caffeine self-administration under a limited range of conditions (Griffiths and Woodson 1988). Low and high doses of caffeine, in the psychomotor-activating range, produce taste and place preference and aversion, respectively (Steigerwald et al. 1988; Brockwell et al. 1991; Myers and Izbicki 2006). Previous caffeine consumption allows adaptation to the aversive effects and facilitates taste preference with high doses (Myers and Izbicki 2006). Similarly, humans also develop taste preference with caffeine, but a consistent finding is that they do not develop preference for a caffeine-paired flavor unless they are at least moderate daily caffeine consumers and unless flavor-caffeine pairing occurs after abstinence long enough to produce withdrawal symptoms (Yeomans et al. 1998; Chambers et al. 2007). Indeed, the American Psychiatry Association (2013) has just accepted "caffeine withdrawal" as a clinical diagnosis. Its symptoms include headache, marked fatigue or drowsiness, dysphoric or depressed mood or irritability, difficulty concentrating, and flu-like symptoms. Negative reinforcement seems therefore to play an additional role in caffeine use (Garrett and Griffiths 1997; Yeomans et al. 1998; James and Rogers 2005; James and Keane 2007). Nevertheless, a recent study showed that caffeine produces significant taste preference regardless of usual caffeine intake (Panek et al. 2013), without implying "withdrawal reversal" (see below).

Following recommendation from Hasin et al. (2013), the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*; American Psychiatry 2013) combined the *DSM-IV* categories of "Substance Abuse" and "Substance Dependence" into a single disorder, "Substance Use Disorder" (SUD), which is measured on a continuum from mild to severe. Each specific substance (except for caffeine) is addressed as a separate disorder (e.g., alcohol use disorder, cocaine use disorder, etc.), but nearly all substances are diagnosed based on the same criteria. Drug craving is added to the list and problems with law enforcement are eliminated because of cultural considerations. For the diagnosis, individuals must fulfill at least two of the following criteria: (1) substance used in larger amounts or over longer periods than intended; (2) a persistent desire or unsuccessful effort to control use; (3) a great deal of time spent obtaining, using, or recovering from the substance; (4) craving the substance; (5) substance use interfering with ability to fulfill major obligations; (6) substance use despite social problems related to use; (7) important occupational or social activities given up

because of substance use; (8) recurrent use in situations when it is physically hazardous; (9) substance use despite harm; (10) tolerance; and (11) withdrawal. The *DSM-5* suggests using the number of criteria met as a general measure of severity, from mild (two to three criteria) to moderate (four to five criteria) and severe (six or more criteria).

DSM-5 does not include a diagnosis of "caffeine use disorder," although it is included in section III: conditions for further study, "to stimulate research that will determine the reliability, validity and prevalence of caffeine use disorder based on the proposed new established diagnostic schema." The proposed diagnostic schema proposed for caffeine use disorder differs from that of all other SUDs and requires the presence of at least criteria 2, 9, and 11 mentioned above. According to the *DSM-5*, this higher threshold is intended to prevent overdiagnosis of caffeine use disorder given the prevalence of non-problematic caffeine use in the general population (American Psychiatry 2013). Even though there is a substantial amount of studies and reports indicating that a subset of caffeine users develops clinically significant symptoms severe enough to seek treatment (Juliano et al. 2012; Budney et al. 2015), there is no agreement about the real health danger upon caffeine regular consumption (Addicott 2014). The difficulties in accepting caffeine use disorder parallel the preclinical evidence for the relatively mild reinforcing effects of caffeine as compared to those of prototypical psychostimulants.

The differences between the efficacy of caffeine at inducing psychomotor activation, reinforcing effects and putatively SUD, as compared with other drugs, can be attributed to several factors coming from both sides. On one side, caffeine does not produce such a strong dopamine activation as that produced by prototypical psychostimulants. Furthermore, caffeine is aversive at doses that otherwise could potentially promote abuse. On the other side, although apparently caffeine produces stronger locomotor activation than alcohol, THC, barbiturates, and opioids, these addictive drugs have depressant effects that depend on different mechanisms which mask their potential locomotor-activating effects. This interpretation is particularly supported by recent studies on interactions between caffeine and alcohol (see below). We can assume than drug-induced activation of striatal dopamine receptors implies reinforcing effects, but not automatically SUD liability. Self-administration in animals and SUD in humans depend on a strong and fast activation of dopaminergic neurotransmission (Volkow et al. 2011). Prototypical psychostimulants such as amphetamine or cocaine, as well as cathinones, the emerging family of synthetic chemicals found under the marketed term "bath salts" (Lehner and Baumann 2013), produce their powerful pharmacological effects by a presynaptic mechanism, interacting with the dopamine transporter (DAT). This causes a fast and pronounced increase of extracellular dopamine, which leads to a pronounced activation of dopamine receptors. As mentioned before, apart from potentiating the effects of endogenous dopamine by adenosine-dopamine receptor interactions, caffeine also produces dopamine release (Solinas et al. 2002; Quarta et al. 2004a, b). However, this is a relatively small effect as compared to prototypical psychostimulants and it seems to be particularly evident in the most medial and dorsal part of the striatum (Borycz et al. 2007).

Paraxanthine, the main metabolite of caffeine in humans, is also a non-selective adenosine receptor antagonist, and it has been recently reported to induce stronger psychomotor activation, measured as locomotion, and striatal dopamine-releasing effects than caffeine (Orrú et al. 2013). It was found that part of the pharmacological effects of paraxanthine is adenosine independent (related to selective inhibition of cGMP-preferring phosphodiesterases), and it was suggested that it could indirectly contribute to the reinforcing effects of caffeine (Orrú et al. 2013). Nevertheless, in experiments with intracranial self-stimulation, caffeine but not paraxanthine increased reward-oriented behavior (Lazenka et al. 2015). Cocaine, amphetamine, and caffeine increased total, reinforced, and non-reinforced responding, but paraxanthine increased only total responses and non-reinforced responses (Lazenka et al. 2015). As discussed by Lazenka et al. (2015), in contrast to their study, caffeine did not facilitate intracranial self-stimulation in previous studies by another research group that used a different procedure (autotitration procedure; Mumford and Holtzman 1990, 1991; Mumford et al. 1988). The limited range of conditions across which caffeine produces a facilitation of intracranial self-stimulation resembles the limited range of conditions across which caffeine maintains self-administration (Griffiths and Woodson 1988) and provides additional evidence for the weak abuse-related effects of caffeine relative to other psychostimulants, such as amphetamine or cocaine. The clear dissociation between paraxanthine-induced locomotor activation and facilitation of reward-oriented behavior is certainly unique, claiming for an additional effect of paraxanthine and maybe caffeine in a lower locomotion integrative center. In fact, it has recently been reported that caffeine stimulates locomotor activity in the rat spinal cord, by a mechanism involving A_1-D_1 receptor interactions (Acevedo et al. 2016).

We should not leave out one final consideration about the very prevalent consumption of caffeine by humans. Otherwise, it is usually inferred as only related to its dopamine-related psychomotor (reward-oriented behavior) and reinforcing (positive and negative) effects. It is about its potent arousal effects, which depend on the specific ability of caffeine to counteract the effects of endogenous adenosine on the ascending arousal systems (see above). We get into the controversial field of the potential attention- and performance-enhancing properties of caffeine, also dependent on the activity of the ascending arousal systems. This takes us back to the reinforcing effects, to negative reinforcement. First, as mentioned above, strong tolerance develops to the striatal A_1 receptor-mediated psychomotor and dopamine-releasing effects of caffeine upon continuous

exposure or repeated daily administration (Holtzman and Finn 1988; Garrett and Holtzman 1995b; Howell and Landrum 1997; Karcz-Kubicha et al. 2003; Quarta et al. 2004a). Now the question is if tolerance also develops to the A_1 receptor-mediated arousal effects of caffeine. In fact, in the experimental animal, sleep deprivation promotes the same biochemical changes observed during repeated treatment or continuous exposure with caffeine, increased adenosine levels (see above), and upregulation of A_1 receptors, which correlate with sleepiness (Elmenhorst et al. 2009; Kim et al. 2012). Also, in humans, sleep deprivation has been shown to increase the density of A_1 receptors in the prefrontal cortex (Elmenhorst et al. 2007). Thus, these mechanisms must play an important role in the sleepiness, marked fatigue, and drowsiness of caffeine withdrawal. Therefore, an important component of the improvement in attention, performance, and wakefulness by caffeine in humans could be explained by relieving withdrawal symptoms, by withdrawal reversal (James and Rogers 2005; James and Keane 2007). Nevertheless, the same as for taste preference experiments (Panek et al. 2013), better controlled studies are providing evidence for arousal effects of caffeine that are independent of the withdrawal reversal (Addicott and Laurienti 2009), which would also fit with the preclinical studies indicating an additional role of A_{2A} receptors in the arousal effects of caffeine and the lack of tolerance to A_{2A} receptor-dependent caffeine mechanisms (see above).

The real danger: caffeine potentiates the addictive and toxic effects of drugs of abuse and could increase vulnerability to SUD

While more clinical research needs to be done to determine if caffeine use disorder can adhere to the general scheme of SUD and about the real contribution of arousal/withdrawal reversal in caffeine use, there is at present no reasonable doubt in the literature about the fact that a rising real societal danger of caffeine is its association with other drugs that fulfill the *DSM-5* criteria for SUD. Caffeine is a unique psychostimulant endowed with the capacity to significantly potentiate the effects of prototypical psychostimulants and all other drugs of abuse. Back to the striatal A_{2A}-D_2 receptor heteromer model, a prototypical psychostimulant, an indirect dopamine receptor agonist such as amphetamine or cocaine leads to a predominant D_2 versus A_{2A} receptor signaling, with a predominant adenylyl-cyclase A_{2A}-D_2 receptor interaction, leading to psychomotor activation (Fig. 3(B)). By blocking the A_{2A} receptor, caffeine counteracts the remaining brake that endogenous adenosine imposes on D_2 receptor signaling, which results in a maximal D_2 and minimal A_{2A} receptor signaling: a maximal psychostimulant effect (Fig. 3(G)). Furthermore, presynaptic mechanisms cannot be excluded, such as the recently reported ability of caffeine to potentiate dopamine release induced by the amphetamine derivative 3,4-methylenedioxymethamphetamine, MDMA or "ecstasy" (Górska and Gołembiowska 2015).

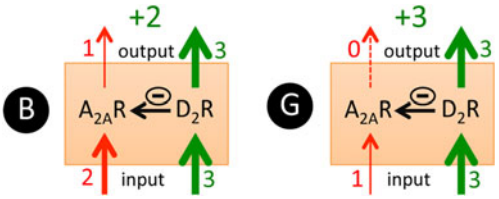

Fig. 3 Model of the striatal A_{2A}-D_2 receptor heteromer as a main mechanism for caffeine-induced potentiation of the psychomotor-activating and reinforcing effects of prototypical psychostimulants. The addition of caffeine or/and A_{2A} receptor antagonist to an indirect dopamine receptor agonist, such amphetamine or cocaine (*B*), can potentially lead to the maximal psychomotor activation driven by the A_{2A}-D_2 receptor heteromer (*G*), as well as the consequences of repeated D_2 receptor-mediated activation, such as behavioral sensitization. See legend to Fig. 1 and text for details

Acutely, caffeine administration has been shown to dose-dependently augment the psychomotor effects of prototypical psychostimulants, such as cocaine or amphetamine, as measured with locomotor activity (Andén and Jackson 1975; White and Keller 1984; Misra et al. 1986), stereotyped behavior (Klawans et al. 1974), and also reward/drug-oriented behavior (Worley et al. 1994; Schenk et al. 1994, 1996). In this case, the reward is the drug of abuse and the psychomotor effects are measured as an increase in drug self-administration or reinstatement of the extinguished self-administration. Reinstatement (stress, drug, or context induced) is commonly used as a measure of drug-seeking behavior. Furthermore, caffeine was shown to partially generalize and to potentiate the discriminative-stimulus effects of cocaine, amphetamine, or methamphetamine (Schechter 1977; Gauvin et al. 1990; Young et al. 1998; Munzar et al. 2002). Drug-discrimination techniques in rodents and primates have been commonly used to study abuse-related effects by establishing the interoceptive effects of a training drug (e.g., cocaine) as a cue for performing a specific operant response (e.g., lever pressing reinforced by food). During training with this protocol, pressing one lever is reinforced when the training drug is injected before the start of the session, and responding on a second lever is reinforced when vehicle is injected before the session. Lever choice during test sessions can then be used as an indication of whether a drug has effects similar to the training drug (generalization) or whether it modifies the effects of the training drug (Solinas et al. 2006). As expected, the same potentiating effects of caffeine on drug seeking and drug discrimination have been documented for selective A_{2A} receptor antagonists (Justinova et al. 2003; O'Neill et al. 2012).

Significantly, caffeine also potentiates the psychomotor effects of prototypical psychostimulants upon repeated treatment or continuous exposure, which is most probably related to the association of cross-sensitization (see above) with the

lack of cross-tolerance (Jain and Holtzman 2005). Thus, repeated treatment or continuous exposure of caffeine has been shown to augment the psychomotor effects of cocaine or amphetamine, as measured with locomotor activity (Schenk et al. 1990; Gasior et al. 2000), turning behavior (Cauli et al. 2003), and reward/drug-oriented behavior (Horger et al. 1991; Jaszyna et al. 1998). Using the drug-discrimination paradigm, Goldberg's research group also demonstrated that continuous exposure to caffeine is associated with tolerance to the ability of A_1 but not A_{2A} receptor antagonists to potentiate the discriminative-stimulus effects of cocaine or amphetamine (Justinova et al. 2009). Lastly, co-administration of caffeine or an A_{2A} receptor antagonist has been shown to potentiate cocaine-induced sensitization of psychomotor activity (Filip et al. 2006; Prieto et al. 2015). Altogether, preclinical data strongly suggest that, acutely or chronically consumed, caffeine potentiates the psychostimulant effects of prototypical psychostimulants.

Apart from coffee, tea, and other caffeine-containing plant extracts, caffeine is found in many commercially available products such as energy drinks, which may be consumed with other drugs in recreational drug use settings (Reissig et al. 2009). Another actual threat is the very common use of caffeine as an adulterant in illicit drug preparations (Cole et al. 2011; López-Hill et al. 2011; Seely et al. 2013), particularly with cocaine, amphetamine derivatives, and synthetic cathinones (Seely et al. 2013; López-Hill et al. 2011). Caffeine was found to be a major adulterant in coca paste seized samples and demonstrated to significantly potentiate the acute psychomotor effects and sensitization induced by those samples administered to rats (López-Hill et al. 2011; Prieto et al. 2015). Also, unambiguous preclinical data have shown that caffeine increases not only the pharmacological effects but also the toxic effects of prototypical psychostimulants, in particular the acute toxicity of substituted amphetamines, such as MDMA and 3,4-methylenedioxyamphetamine (MDA), manifested as high core body temperature, tachycardia, and increased mortality (reviewed in Vanattou-Saïfoudine et al. 2012). Also, upon repeated co-administration, caffeine enhances MDMA-induced neuroinflammatory glial reactivity (Khairnar et al. 2010). In summary, although generally thought to be mostly listed as a bulk adulterant (Cole et al. 2011), the overwhelming preclinical evidence for the enhancing psychomotor and toxic effects of other recreational psychostimulants by caffeine calls for the urgent need of control or at least for increasing social awareness.

Caffeine and alcohol constitute another alarming combination with increasing popularity, particularly the association of energy drinks with alcoholic beverages among the adolescent and young adult population (O'Brien et al. 2008; Reissig et al. 2009; Peacock et al. 2014; McKetin et al. 2015). First, energy drinks and caffeine beverages in general facilitate alcohol drinking and related harms by reducing its effects on intoxication. Thus, caffeine attenuates the "unwanted" somnogenic and ataxic effects of alcohol, which depend on its ability to increase the extracellular concentration of adenosine (by direct inhibition of the equilibrative nucleoside transporter ENT1) and activate A_1 and A_{2A} receptors that inhibit the ascending arousal systems and A_1 receptors localized in the cerebellum and other brain areas. This adenosine increase occurs under conditions of acute alcohol intake (reviewed in Ferré and O'Brien 2011). Second, we recently proposed that, based on mechanisms involving the striatal A_{2A}-D_2 receptor heteromer (Fig. 3), caffeine should strongly potentiate the "wanted" effects of alcohol, its psychostimulant effects (Ferré and O'Brien 2011). In fact, recent research suggests that energy drinks combined with alcohol increase the "desire" to drink (Marczinski et al. 2013). It is widely believed that the reinforcing effects of alcohol depend on its ability to produce striatal dopamine release by direct and indirect mechanisms that increase the activity of dopamine neurons (Tupala and Tiihonen 2004; Morikawa and Morrisett 2010). Under conditions of acute alcohol intake, the increased adenosine tone tends to counteract its psychomotor and reinforcing effects, which should then be strongly potentiated by caffeine (Ferré and O'Brien 2011). Recent experiments in mice have provided strong evidence for this hypothesis, showing that combination of caffeine and alcohol produces a stronger psychomotor activation (locomotor activity) than either drug administered alone (Hilbert et al. 2013). The same research group recently reported that when given by oral gavage, repeated co-exposure to alcohol and caffeine produces a much larger effect than repeated exposure to either drug alone (May et al. 2015). Under conditions of chronic alcohol intake (alcohol use disorder), in contrast to the acute situation, there is a reduced adenosine tone. In fact, chronic alcohol exposure results in an increased expression of ENT1 and, therefore, a decrease in alcohol-mediated inhibition of ENT1 (Parkinson et al. 2009). This decrease in the adenosine tone is at least partially responsible for the tolerance to the acute effects of alcohol and also to the main symptoms of alcohol withdrawal, such as insomnia, anxiety, and seizures (Concas et al. 1994; Gatch et al. 1999; Prediger et al. 2006). In fact, a study with human subjects showed that a history of combined alcohol and caffeine administration increases alcohol tolerance compared with a history to either drug alone (Fillmore 2003). In addition, a chronically reduced adenosine tone should potentiate the psychomotor and reinforcing effects of alcohol, its psychostimulants effects. Altogether, the clinical and preclinical data on caffeine- and adenosine-alcohol interactions provide nice support for the psychomotor stimulant theory of addiction, which would predict that counteracting the adenosine-mediated psychomotor depressant ("unwanted") effects of alcohol by decreasing adenosine (chronic alcohol use) or blocking adenosine receptors (caffeine) should disclose its potentially very strong psychostimulants effects.

A final consideration of the potential social danger of caffeine is its use by children and adolescents. The availability of caffeine in the young population is a source of growing concern (Temple 2009). Reviews in the literature have suggested that children may not be more sensitive than adults to caffeine and that perceived differences are due to lower body weight (Nehlig et al. 1992; Leviton 1992). However, animal models, which offer the possibility of controlled longitudinal studies, are bringing a completely different picture. First, in adolescent rats, the acute psychomotor-activating effects of caffeine are stronger and its depressant effects (with higher doses) milder than those in adult rats, suggesting that adolescents can consume higher amounts (Marin et al. 2011). Second, after chronic treatment with caffeine, both tolerance to the acute psychomotor-activating effects and withdrawal-induced psychomotor depression were significantly more pronounced in adolescent rats, suggesting that adolescents can be more dependent on caffeine (withdrawal reversal) than the adult population (Rhoads et al. 2011). Finally, caffeine consumption by adolescent rats increases the psychomotor-activating effects of cocaine in the adult rats (measured with locomotor activity and place preference). Significantly, the behavioral results were associated with upregulation and downregulation of striatal D_2 and A_{2A} receptors, respectively (O'Neill et al. 2015). This would imply that caffeine use by adolescents could produce long-lasting neurochemical changes in the brain (in adenosine-dopamine neurotransmission) that can increase vulnerability to SUD, as at least supported by a controlled study using an epidemiologic and monozygotic-twin analysis (Kendler et al. 2006).

Conclusion

The knowledge accumulated during the last three decades about the role of the ascending dopamine systems in psychomotor activity and reinforcement, the identification of the ascending arousal systems and their interconnections, the role of adenosine and adenosine receptors in the modulation of ascending dopamine and arousal systems, and the discovery of the adenosine-dopamine receptor heteromers allows us to understand the mechanisms behind the psychostimulant effects of caffeine. We are now able to evaluate more directly, both in humans and the experimental animal, unequivocal main pharmacological targets of caffeine, such as the A_{2A}-D_2 receptor heteromer (Bonaventura et al. 2015; Volkow et al. 2015). This should help us determine the real societal values and dangers of such a unique psychostimulant, the most-used psychoactive drug in the world.

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