Chapter 16
Interactions of Cannabis and Amphetamine-Type Stimulants

Simone Tambaro and Marco Bortolato

Abstract Amphetamine-type stimulants (ATSs) are a large family of substances of abuse, characterized by well-known mood- and performance-enhancing properties. This class encompasses several high-potency stimulants and entactogens, such as the precursor compound *d*-amphetamine (AMPH), its synthetic *N*-methylated derivatives methamphetamine (METH) and 3, 4-methylenedioxy-*N*-methylamphetamine (MDMA, or "ecstasy"), as well as novel designer drugs, based on substituted forms of the natural alkaloid cathinone. ATSs (and in particular METH) are among the most commonly abused substances worldwide, second only to *Cannabis sativa*; indeed, the rate of concurrent consumption of METH and cannabis has been increasing over the last decade, particularly among adolescents. Anecdotal evidence suggests that marijuana may offset some unpleasant subjective effects of ATSs, such as anxiety and paranoia. Both drugs have been shown to increase schizophrenia vulnerability in young vulnerable individuals, raising the possibility that their concurrent intake may have synergistic effects with respect to the development of psychotic manifestations. In addition, the combination of these two substances may affect their subjective effects and exacerbate their abuse liability. Although current evidence on the neurobiological interactions of cannabis and ATSs remains mostly elusive, initial studies in animal models suggest that the cannabinoid system may play a relevant role in the motivational and addictive properties of ATSs; furthermore, cannabinoids may modify the behavioral effects and even attenuate some untoward long-term consequences of ATSs. In this chapter we review the available evidence on these potential interactions and outline some key mechanisms that may account for the mutual modulatory influence of these substances.

Keywords Cannabis · Amphetamine-type stimulants · Methamphetamine · Dopamine · CB_1 receptors · Neuroprotection

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P. Campolongo, L. Fattore (eds.), *Cannabinoids and Modulation of Emotion, Memory, and Motivation,* DOI 10.1007/978-1-4939-2294-9_16

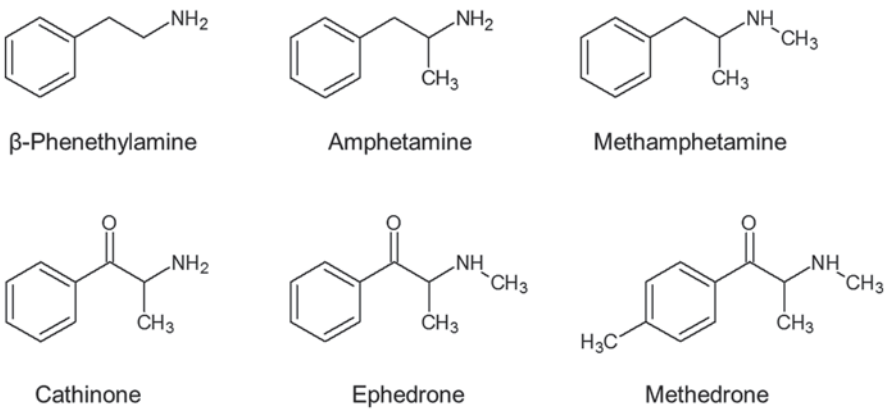

Fig. 16.1 Chemical structures of β-Phenethylamine and some of the major amphetamine-type stimulants (ATSs)

Introduction

Amphetamine-type stimulants (ATSs) are a large family of psychoactive drugs characterized by a common phenylethylamine core structure. The precursor of this class, d-amphetamine (AMPH; 1-phenylpropan-2-amine) and its N-methylated derivative methamphetamine (METH; N-methyl-1-phenylpropan-2-amine), were respectively synthesized in 1887 [1] and 1893, and marketed as decongestants under the commercial names of *Benzedrine* and *Methedrine* [2]. Following the discovery and characterization of the psychostimulant properties of these drugs, they were originally proposed and used for numerous illnesses, such as depression, migraine, alcoholism and obesity[1]. With the growing diffusion of AMPH and METH as therapeutic agents, it was recognized that high doses of these agents could lead to prominent euphoria and excitement, disinhibition, increased libido and arousal, sense of invincibility, fatigue resistance and sleeplessness; furthermore, it soon became apparent that both drugs had a high addiction liability, and that their abuse was associated with a higher risk for mania and psychosis. Nowadays, the class of ATSs is known to encompass a large variety of different synthetic compounds (the structures of the main ATSs are represented in Fig. 16.1, as well as the natural alkaloids ephedrine and cathinone, respectively obtained from the plants *Ephedra sinica* and *Catha edulis*. The behavioral properties of the ATSs vary depending on the chemical structure; for example, the effects of 3, 4-methylenedioxy-methylamphetamine (MDMA, also known as "ecstasy) and similar compounds induce effects typically

[1] Nowadays, the therapeutic applications of ATSs are mostly limited to low-potency compounds, which carry a very limited liability for dependence. Notably, low doses of the dextrorotatory enantiomers of AMPH and METH are still approved by the Food and Drug Administration for the treatment of narcolepsy and attention-deficit hyperactivity disorder (ADHD).

different from those elicited by AMPH and METH, typically described as an enhances sense of emotional closeness and empathy.

METH features greater potency and a significant longer half-life than cocaine or other common stimulants (ranging from 10–30 h) [3]; because of these properties, its misuse for recreational purposes (generally by smoking or snorting) gained momentum in the 1960s and has reached the proportions of a veritable epidemic in the past decades [4], particularly among adolescents of North America, East Asia and Oceania [5–9]. A recent report released by the United Nations Office on Drugs and Crime has ranked METH and other ATSs as the world's most widely abused type of illicit substance after cannabis [10].

Until the late 1980s, the concomitant abuse of cannabis products and ATSs was generally regarded as a relatively infrequent phenomenon [11], possibly due to the divergence in the sociocultural milieux traditionally associated with the consumption of either substance. In the early 1990s, however, this trend was rapidly reversed by the introduction of large amounts of high-purity METH by Mexican drug cartels in the illicit market of the Western and Midwestern regions of the United States. The increased availability of pure METH at lower prices led to its growing popularity among the local communities of cannabis users [12]. By 2002, it was estimated that cannabis was the most common secondary substance of abuse among METH-dependent individuals [13]. In striking contrast with the skyrocketing proportion of the comorbid abuse of cannabis and METH, research on the interactions of these two substances has considerably lagged behind. To the date of this writing (December 2013), only few systematic clinical studies on the combined effects of ATSs and cannabis have been published in peer-review publications.

In this chapter, we will outline the available evidence on the interactions of cannabis and ATSs, as well as their underlying neurobiological mechanisms. In particular, we will mainly focus on the interaction of AMPH and METH with the two most abundant ingredients of cannabis, namely its main psychoactive alkaloid Δ9-Tetrahydrocannabinol (THC), and cannabidiol (CBD). Nevertheless, it is worth noting that similar effects and mechanisms are predicted for the interaction of newly-developed synthetic cannabinoids ("Spice") and new-generation ATSs ("Bath salts"). The latter, which include mephedrone, methylone, methcathinone, amfepramone and pyrovalerone, are mainly synthetic cathinone derivatives [14]. Conversely, synthetic cannabinoids (including bicyclic compounds, benzopyrans and aminoalkylindole derivatives) [15] were originally developed as experimental drugs, but have recently reached the illicit market (see Chap. 10 of this book). Unfortunately, these compounds are often sold in combination; in particular, it has been recently reported that new drugs that combine the pharmacological properties of both categories may have already been developed [16]. This alarming scenario raises the urgency of a better understanding of the interactions of cannabinoids and ATSs, particularly with respect to their behavioral and toxic consequences.

Effects and Mechanisms of Action of AMPH and METH

Although the clinical and behavioral effects of AMPH and METH have been documented for longer than 50 years, their mechanism of action still remains partially elusive. Several molecular mechanisms of AMPH and METH are posited to mimic the actions of their endogenous analog β-phenylethylamine (β-PEA), a naturally occurring trace amine that acts as a neuromodulator of monoamine neurotransmitters, such as dopamine (DA), norepinephrine (NE) and serotonin (5-HT) [17]. β-PEA is mainly present in monoaminergic neurons, where it is synthesized by decarboxylation of the amino acid phenylalanine [17] and metabolized by monoamine oxidase (MAO) B [18]. Although the synthesis of β-PEA is thought to occur with a rate similar to that of DA and NE, its concentration are significantly lower than those of catecholamines, because of its significantly higher metabolism by MAO B [19]. Physiological concentrations of β-PEA play an important role in the modulation of DAergic neurotransmission, by inducing DA release, inhibiting its reuptake and limiting the responses of D_2 autoreceptors [20–23]. Most of these actions are ascribed to the activation of the main receptor of β-PEA, named trace amine associated receptor 1 (TAAR1) [24]. This G_s-protein-coupled receptor appears mainly located within intracellular membranes [25, 26] of monoaminergic neurons [24, 27].

Effects of AMPH and METH on DA Neurotransmission

In addition to their analogy to β-PEA, AMPH and METH bear a strong structural resemblance with DA, and compete with this neurotransmitter for their uptake into the presynaptic terminals of DAergic neurons by the DA transporter (DAT) [28, 29]. Indeed, the intracellular transport of AMPH and METH enhances DA concentrations in the extracellular space by reducing its uptake and facilitating its release through DAT-mediated antiport [30–32] (Fig. 16.2). Once AMPH and METH are carried in the cytosol, they activate TAAR1 [33], stimulating the protein kinases A (PKA) and protein kinases C delta (PKCΔ) [34–36]. The ensuing phosphorylation of DAT leads to its endocytosis, accumulation in endosomes and reduced recycling [37].

Although AMPH and METH are potent TAAR1 agonists, this receptor is not thought to play a primary role in the ability of these drugs to enhance the activity of DAergic neurons; accordingly, TAAR1 activation has been shown to reduce, rather than increase, the firing of DAergic neurons [38]. The mechanisms that likely support the psychostimulant properties of AMPH and METH are based on their ability to bind to the vesicular monoamine transporter 2 (VMAT2), which results in the inhibition of DA transport within the vesicles [39]. The inactivation of VMAT2 has been shown to counter some of the phenotypical effects of METH and AMPH, such as the enhancement of DA efflux [40–43], as well as the behavioral effects of these drugs [44, 45]. A third mechanism that contributes to the enhancement of extracellular DA levels by AMPH and METH is afforded by their inhibition of MAOs, which catalyze the metabolism of DA and other monoamines [46, 47].

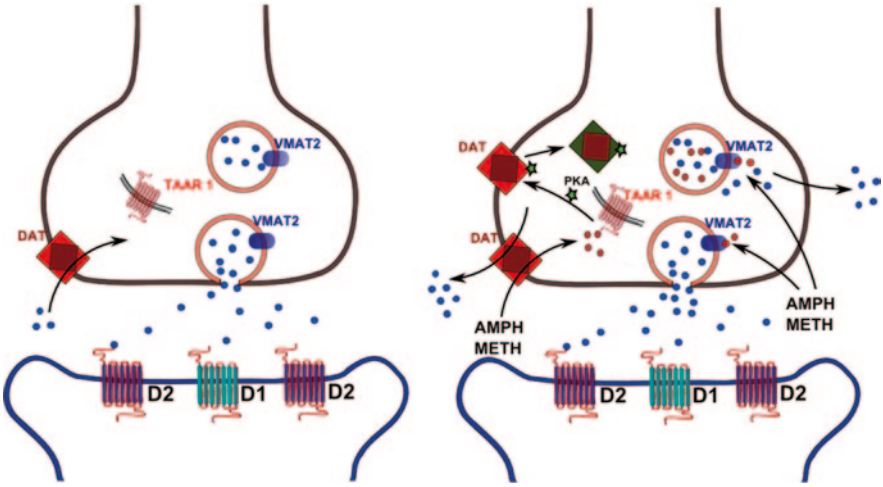

Fig. 16.2 Schematic model of the actions of amphetamine-type stimulants (ATSs) in the presynaptic terminal of the dopaminergic neuron. **a** In physiological condition DA is released in the synaptic cleft by a calcium-dependent system. The uptake is accomplished by a membrane carrier (1), which can transport DA into and out of the terminal depending on the existing concentration gradient. Cytoplasmic DA is transported into storage vesicle by vesicular monoamine transport 2 (VMAT2). **b** ATSs enter the presynaptic bouton across through DAT. AMPH and METH enhance DA concentrations in the extracellular space by reducing its uptake and facilitating its release through DAT-mediated antiport. Once AMPH and METH are carried in the cytosol, they activate TAAR1, stimulating the protein kinases PKA and PKC (not represented). The phosphorylation of DAT leads to its endocytosis. AMPH and METH interfere also with the vesicular carrier VMAT2, thereby reducing the intravesicular uptake of DA and facilitating its release in the cytosol

The combination of the mechanisms outlined above results in a general enhancement of DA neurotransmission in the nigrostriatal and mesocorticolimbic projections, the two main pathways of the DAergic system that regulate movement and reward-associated responses. These functions account for the marked stimulant effects of these substances, which lead to the enhancement of motoric and motivation-based activity.

It is worth noting that the effects of AMPH and METH are largely due to the increase of DA *volume transmission,* one of the two main modalities of DA neurotransmission. Volume transmission consists in the non-vesicular release of DA from non-junctional varicosities of its neurons, leading to the activation of DAergic receptors in the extrasynaptic and perisynaptic space [48–51]. In the striatum and nucleus accumbens, the fine regulation of the balance between volume and synaptic transmission of DA is considered to play a key role in encoding informational salience with respect to locomotor modulation or the execution of motivated behaviors.

Low doses of AMPH lead to a modest increase in volume transmission, which may be essential to enhance focused attention. Conversely, higher doses of ATSs are likely to lead to a more robust DA spillover, which may facilitate the development

of psychotic responses through a generalized attribution of salience to irrelevant information and thoughts [52]. This impairment leads to a deficit of the signal-to-noise ratio, leading to deficits of sensorimotor gating and information filtering [53]. In confirmation of this theory, only high doses of AMPH have been found to result in the disruption of the prepulse inhibition of the startle reflex, the most common operational index for the measurement of sensorimotor gating [54].

The role of AMPH and METH in the modulation of attentional and cognitive processes may reflect the distribution of the two main classes of DA receptors, D_1 and D_2, in the nucleus accumbens and striatum. Low doses of AMPH are likely to lead to activation of D_2 receptors in the postsynaptic terminal or in direct contiguity with the presynaptic bouton. Accordingly, low doses of AMPH has been shown to affect D_2, but not D_1 binding [55]. The increase in DA release corresponding to these dosages may not be sufficient to stimulate D_1 receptors, which are generally localized in spines and dendrites of medium-spiny GABAergic neurons in proximity of glutamatergic synapses, further away from the synapse than D_2 receptors [56–60]. Conversely, higher doses of AMPH may lead to the joint activation of extrasynaptic D_1 and D_2 receptors. The hyperlocomotion and sensorimotor gating deficits of AMPH have been shown to be dependent on either class of receptors [61–65], even though their differential role may reflect specific differences in receptor distribution and sensitivity among different strains and species.

Higher doses of ATSs are thought to produce a marked increase of striatal extrasynaptic and perisynaptic DA levels [66]. The D_1 receptors are actually essential to induce a prolonged and robust excitatory action in the extrasynaptic terminals of the striatum [67]. Presynaptic D_2 receptors have been shown to mediate effects not only as DA autoreceptors, but also on γ-aminobutyric acid (GABA) [68–70] and glutamate [71] in the striatum. Thus, it is tempting to hypothesize that a robust DA spillover may have effects also on the release of GABA and glutamate through activation of these receptors. Future studies are needed to confirm this possibility and evaluate its functional significance.

Non-DAergic Mechanisms of AMPH and METH

The actions of AMPH and METH as analogs of β-PEA have repercussions also on the other monoamine neurotransmitters, namely 5-HT and NE. Both drugs have been found to reduce the uptake and increase the extracellular levels of these neurotransmitters, and these mechanisms have been shown to play an essential role in the behavioral effects of ATSs [72–74]. However, the role of TAAR1 in these processes has not been fully clarified yet. While it is assumed that the actions on 5-HT neurotransmission may be similar to those observed for DA, the mechanisms may differ with respect to NE. For example, the internalization of NE transporter has not been observed in response to AMPH. The effects of ATSs are likely not limited to the monoaminergic systems, but are likely to involve also other neurotransmitters, such as glutamate and GABA [75–77]. The details of these processes, however, await further clarification.

Neurotoxic Effects and Mechanisms of METH

One of the most problematic consequences of METH lies in the permanent damage of midbrain, striatal and cortical neurons, which leads to long-lasting depletions of striatal DA and 5-HT [78, 79]. The molecular mechanisms supporting the neurotoxic effects of METH are not fully understood, but they are generally thought to be related to excessive concentrations of DA (and, possibly, 5-HT) in the cytosol. In this compartment, DA undergoes non-enzymatic oxidation with the production of quinones and other oxyradicals [80, 81], which trigger oxidative stress, mitochondrial dysfunctions and the formation of oligomeric protein aggregates of DAT as well as α-synuclein [82–85], ultimately leading to the death of DAergic cells. One of the most common and dangerous effects of METH neurotoxicity is a life-threatening hyperthermia, which accompanies alterations of the blood-brain barrier and brain edema [86], and is a primary cause of lethality following METH overdose and toxicity [87, 88].

The neurotoxic mechanisms of METH, albeit still partially unclear, have been recently shown to be inversely related to the availability of VMAT2 [43, 89, 90] and involve the activation of D_2 receptors [91]. It should also be noted that METH-induced neurotoxicity has been shown to involve glutamatergic excitotoxicity in the striatum [92], likely due to the enhancement of glutamate level in the striatum, which may potentiate the oxidative stress induced by DA [93]. Other METH-induced neurotoxic mechanisms appear to involve the activation of caspase 3 and other apoptotic mechanisms [94–96].

Interactions of Cannabis and ATSs

The well-documented role of ATSs and cannabis in the pathogenesis of psychiatric disorders, ranging from anxiety-spectrum to psychotic and cognitive disorders [97, 98] raises serious concerns about the sequelae of their combined use. This issue may become even more problematic with the recent diffusion of synthetic designer drugs in both categories, which are often sold as mixtures.

As mentioned above, marijuana and other hemp products are the most common secondary substances of abuse among METH users [13], and, in particular, adolescents. This scenario is really concerning, in view of well-documented evidence linking both substances to psychotic manifestations in youth [99, 100]. Indeed, as widely reviewed in Chapt. 12 of this book, cannabis abuse in adolescence has been highlighted as a key risk factor for schizophrenia for genetically vulnerable individuals [101, 102]. Thus, it is likely that the combined consumption of cannabinoids and ATSs may be particularly dangerous and addictive.

Based on anecdotal reports, it has been suggested that cannabis may prolong and intensify the sensation of euphoria associated with consumption of ATSs [103] as well as other psychostimulants [104]. In addition, the calming and relaxing properties of cannabis may offset some of the psychological untoward consequences

of ATS, such as anxiety and agitation. This possibility is supported by preclinical evidence in rodents subjected to both acute and chronic administration of METH [105]. However, cannabis has been shown to produce variable effects with respect to anxiety [106] and may even exacerbate some of the negative subjective sensations induced by ATSs, such as panic and paranoia.

Pending the expansion of research on the topic, the current state of the art generally relies on the assumption that cannabis may interact with ATSs in a fashion similar to those documented with cocaine, another psychostimulant whose mechanism of action is largely based on the enhancement of DAergic neurotransmission. Indeed, several behavioral and physiological effects of METH resemble those of cocaine. Nevertheless, this vista does not account for key mechanistic differences between cocaine and ATSs: while the latter blocks DA uptake, ATSs also increase the release and inhibit the metabolism of this neurotransmitter. In addition, as mentioned above, METH has a significantly slower clearance and wider brain distribution than cocaine [107]. Because of these differences, METH produces a much more prolonged sensation of "high" than cocaine. In addition, the higher amounts of extra-vesicular DA are likely to result in greater neurotoxicity levels, due to reactive oxygen species (ROSs) from non-enzymatic catabolism of DA.

In the next sections, we will summarize the available evidence on the interactions of cannabis and ATSs and elaborate on their putative mechanisms. This discussion will be preceded by a brief preamble on the endocannabinoid system and its relevance to the mechanisms of cannabis, specifically designed to facilitate the readers who may be unfamiliar with the key neurobiological mechanisms of THC and other cannabinoids. For a more thorough treatment of these topics, however, the interested reader is referred to the excellent reviews by De Petrocellis et al. [108] and Mechoulam and Parker [109].

A Brief Outline on the Endocannabinoid System

Most of the actions of THC are mediated by two major cannabinoid receptors, both coupled to $G_{i/o}$ proteins [110], respectively termed CB_1 [111] and CB_2 [112]. CB_1 receptors are abundantly expressed in the brain and implicated in the majority of the psychotropic actions of cannabis. These receptors are typically localized on the membrane of presynaptic terminals of GABAergic and glutamatergic neurons [113, 114], where they control the release of either neurotransmitter in response to retrograde activation from the postsynaptic terminal [115–118]; furthermore, these receptors are involved in other key plasticity mechanisms, such as short- and long-term synaptic depression [119]. CB_1 receptors also form heteromeric complexes with other G-protein complex receptors, such as dopamine D_2, μ-opioid and adenosine A_{2a} [120–122].

In contrast with CB_1 receptors, CB_2 receptors are abundantly expressed in most peripheral organs (and particularly in immune cells, where they regulate cytokine secretion and modulate cell trafficking) [123]. Although the presence of CB_2 receptors in neurons has been revealed [124, 125], their function remains poorly understood and awaits further characterization.

Cannabinoid receptors are bound by the two endogenous ligands (endocannabinoids) 2-arachidonoylglycerol (2-AG) [126, 127] and N-arachidonoylethanolamine (also termed anandamide) [128].

2-AG acts as a full agonist at both CB_1 and CB_2 receptors, and mediates the mechanisms of short-term control of glutamate and GABA release [116, 117]. Conversely, anandamide acts as a high-affinity partial agonist for both CB_1 and CB_2 receptors. In addition, this endocannabinoid interacts also with the vanilloid channel receptors 1 (TRPV1), which are abundantly distributed in DAergic neurons. Interestingly, TRPV1 receptors are also activated by the main non-psychotropic ingredient of cannabis, CBD, raising the interesting possibility that some of the therapeutic effects of this alkaloid may be mediated by these channels.

Anandamide is synthesized on demand by enzymatic hydrolysis of the membrane phospholipid N-arachidonoyl phosphatidylethanolamine (NAPE), a process catalyzed by several phospholipases [129, 130]. Following release and activation of CB receptors, anandamide is rapidly removed from the synaptic cleft by a carrier-mediated system [131–134] and subsequently hydrolyzed by the membrane enzyme fatty acid amide hydrolase (FAAH) [135–137]. Anandamide appears to be mainly involved in plastic mechanisms such as long-term depression (LTD) [138]. It should also be noted that, in the striatum, 2-AG and anandamide may serve different roles with respect to the release of glutamate and GABA. 2-AG acts preferentially on CB_1 receptors in GABAergic neurons; in fact, the simulation of its synthesis was found to reduce GABAergic, but not glutamatergic neurotransmission [139, 140]. Conversely, anandamide may inhibit the release of glutamate by activating CB_1 receptors in glutamatergic neurons [141].

Effects of METH and Cannabis on Schizophrenia

In comparison with other psychostimulants, such as cocaine, METH consumption is associated with a markedly high schizophrenia risk [100]. This aspect is particularly noteworthy in consideration of its potential interactions with cannabis, the only other substance of abuse that has been unequivocally linked to a significantly higher vulnerability for schizophrenia and other psychotic disorders [99, 100]. Based on this premise, several studies have been recently focused on the possibility of synergistic effects of cannabis and METH with respect to the pathogenesis of schizophrenia. Although the evidence on these interactions is still rudimentary, recent studies have shown that the combined abuse of cannabis and ATSs is indeed associated with an earlier age of schizophrenia onset, in comparison with consumption of either cannabis or ATSs alone [142].

To understand the nature of the interactions of cannabis and METH with respect to schizophrenia, it is useful to briefly review the evidence on the role of the endocannabinoid system in this disease (for an extensive overview of the topic, see [143–145]. Schizophrenia patients have been found to feature elevated anandamide levels in plasma [146] and cerebrospinal fluid (CSF) [144], as well as higher CB_1 receptor density in prefrontal and cingulate cortex [147–149]. Notably, the levels

of CB_1 receptors in schizophrenia patients are down-regulated by antipsychotics [150].

The pathogenic mechanism whereby cannabis and METH may lie to schizophrenia has been posited to lie in DA-induced maladaptive interpretations of contextual cues, which may reflect developmental alterations in adolescence and may be further exacerbated by environmental and psychosocial adversity [151]. Whereas there is general consensus on the primary involvement of DA in the mechanisms supporting METH-induced acute psychotic states [152, 153], the role of this neurotransmitter in cannabis-induced psychosis is more controversial. It has been reported that, in schizophrenia patients, doses of THC that exacerbate psychotic symptoms are associated with a rapid reduction of D_2 receptor binding in the ventral striatum and precommissural dorsal putamen [154, 155]. However, similar phenomena were not observed in healthy volunteers [156]. Furthermore, the psychotomimetic effects of THC are not attenuated by the benchmark typical antipsychotic haloperidol, which acts as a D_2 receptor antagonist. Indeed, this drug was even found to exacerbate some of the cognitive deficits induced by THC, such as distractibility and reduced vigilance [157].

Irrespective of the mechanism, emerging evidence supports that METH's psychotomimetic properties may be modulated by cannabis through activation of CB_1 receptors. A recent genetic study [158] found that the latency to the onset of psychotic responses to METH consumption is associated with variants of a single-nucleotide polymorphism (Rs806379) of the gene CNR1 (encoding the CB_1 receptor). Notably, this gene has been associated with schizophrenia vulnerability in several studies [159, 160]. While preclinical results have suggested that antagonism of CB_1 may attenuate schizophrenia symptoms [161, 162], preliminary clinical trials have failed to support this possibility [163].

Effects of METH and Cannabis on Abuse and Dependence

Another important domain of investigation on the clinical interactions of ATSs and cannabis concerns the establishment of abuse and dependence. Cannabis has long been posited to serve as a "gateway" drug, which may facilitate the subsequent abuse and dependence of other substances [164–166]. This characteristic may be potentiated by METH abuse and dependence, which have been associated with a higher proclivity to engage in risky behaviors [167, 168]. Indeed, the concurrent abuse of cannabis and METH has been recently found to be associated with earlier initiation to ecstasy use [169].

A plausible interpretation for a combined effect of METH and cannabis on the initiation to the use of other drugs is likely to reflect abnormalities in DA striatal neurotransmission, resulting in abnormal decision-making processes related to motivational responses. In keeping with this interpretation, Churchwell and collaborators [170] found higher novelty-seeking and striatal volume in adolescents reporting comorbid abuse of METH and cannabis.

Several lines of evidence suggest that the endocannabinoid system may play a role in the subjective effects of ATSs, and therefore influence the risk for abuse and dependence [171]. Allelic variants of the *FAAH* gene have been associated with the subjective response to AMPH [172], as well as a higher risk for substance abuse and dependence [173, 174]. Similarly, genetic variants of the [AAT]n trinucleotide short-tandem repeat polymorphism of the *CNR1* gene (encoding CB_1 receptors) have been associated with an increased risk for intravenous use of AMPH [175] as well as other drugs [176]. The role of CB_1 receptors in the subjective properties of ATSs is also supported by the finding that its blockade in *Cebus* monkeys reduced the arousal induced by AMPH [177].

The facilitatory role of cannabis with respect to METH abuse and dependence is generally supported by several lines of evidence on rodent models. Indeed, while pre-exposure to THC does not appear to affect the self-administration of AMPH in rats [178], the blockade of CB_1 receptors attenuates METH self-administration [179, 180]. Notably, this effect may not reflect an intrinsic reduction of the rewarding properties of METH, but rather the acquisition and consolidation of the preference for this drug [181, 182], suggesting that the key effect of cannabis may modulate the plastic and adaptive response to repeated administrations of ATSs. In particular, these phenomena are likely to be mediated by CB_1 receptors in the nucleus accumbens, possibly in relation to the modulation of acetylcholine neurotransmission [183, 184]. In keeping with this hypothesized mechanism, CB_1 receptors may also affect the reinstatement of METH self-administration [185, 186]. Notably, CB_1 receptor antagonists have also been shown to reduce METH-induced deficits in operant responding [187] and inhibitory control [188]. Of note, THC has been shown to potentiate the extinction of AMPH-induced conditioned preference learning [189], but this mechanism was not reversed by CB_1 receptor blockade, supporting a possible role of CB_2 receptors.

Role of CB_1 Receptors in the Psychostimulant Properties of ATSs

As mentioned above, the clinical evidence on the role of CB_1 receptors on the psychostimulant effects of AMPH and METH is only limited to anecdotal evidence and indirect inferences based on genetic studies. Conversely, several studies on the topic have been performed in rodent models. In general, the bulk of evidence suggests that CB_1 receptors in the nucleus accumbens may contribute to some of the motor effects of ATSs, including AMPH and METH-induced hyperactivity and stereotyped behaviors [190–193]. These effects are posited to reflect a negative modulatory action on DAergic neurotransmission; in fact, CB_1 receptor blockade has been shown to potentiate, rather than attenuate, the stereotyped behavior induced by co-administration of D_1 and D_2 receptor antagonists [194]; furthermore, activation of CB_1 receptors has been shown to reduce the hyperactivity induced by D_2 receptor stimulation [195]. In apparent contrast with this evidence, several studies have indicated that the genetic inactivation of CB_1 receptors may attenuate the hyperactivity induced by AMPH [162]; these effects, however, have not been con-

sistently replicated [196, 197], possibly in relation to different influences of genetic and environmental vulnerability factors. The alterations of ATS-induced effects in CB_1 knockout (KO) mice may reflect their lower levels of striatal DA [198], as well as abnormalities in D_2 (but not D_1) receptor binding in the striatum [196].

Finally, several studies have shown that CB_1 receptors play a role in the development of motor sensitization to AMPH. Chronic THC administration facilitates this phenomenon [199], while CB_1 receptor inactivation decreases the development of motor sensitization to AMPH [200–202].

Mechanisms of Interactions of Cannabinoids and ATSs

Cannabinoids and ATSs are posited to interact on multiple levels, through a complex array of intersecting mechanisms across several brain regions. In this synoptic overview, we will summarize the best-characterized lines of evidence on the collective implication of these substances on the regulation of DAergic neurotransmission and its behavioral and pathophysiological correlates. Nevertheless, we should point out that these mechanisms are part of a broader network that incorporates the actions of the other neurotransmitters affected by both ATSs and cannabinoids, such as NE and 5-HT. With respect to the role of DAergic pathways, the interplay of cannabis and ATSs is likely related to the endogenous modulatory mechanisms of this system, which involve both trace amines (such as β-PEA) and endocannabinoids as well as their attending receptors in DA neurotransmission and signaling [203–210].

As noted above, although CB_1 receptors are expressed in DAergic neurons [211–213], most of the effects of cannabinoids on DAergic neurotransmission are posited to be the result of indirect mechanisms, primarily mediated by the activation of CB_1 receptors on presynaptic terminals of neighboring GABAergic and glutamatergic neurons (Fig. 16.3). This modulation occurs both around the somata of DAergic neurons in the midbrain, as well as along their terminals, in the dorsal striatum, nucleus accumbens and prefrontal cortex [214]. The actions of cannabinoids mimic the molecular activity of 2-AG and anandamide on the activity of mesolimbic and mesocortical DAergic neurons.

In general, the effects of cannabinoids on the activity of these cells are highly variable, and may follow dose-dependent patterns, likely reflective of the progressive recruitment of different subpopulation of neurons subserving different modulatory roles in relation to DAergic activity. In line with this concept, the loss of GABAergic inhibition in CB_1-positive neurons has been recently shown to counter the DA-releasing properties of AMPH [215]. In addition, the variability of the effects of cannabis depends on a wide set of genetic and environmental vulnerability factors [216], including sex (see Chap. 12 of this book); some of these variable, such as stress, are known to affect the sensitivity to ATSs [217, 218]. In summary, the direction and verse of the modifications of DAergic activity ensuing the co-administration of ATSs and cannabinoids are heterogeneous, depending on specific individual characteristics as well as dose-dependent modalities of action on various circuitries associated with DAergic pathways. In spite of this high variability, pre-

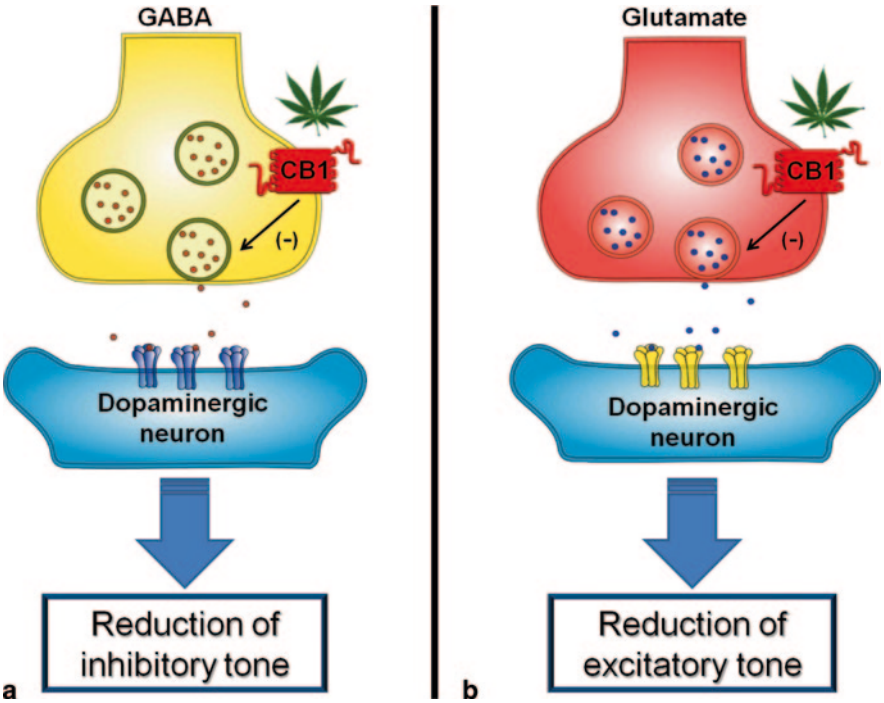

Fig. 16.3 Schematic representation of CB_1 receptor-mediated effects in GABAergic (**a**) and glutamatergic neurons (**b**). Activation of CB_1 receptors in these two neurons exert opposite effects with respect to the modulation of DAergic neurons. This mechanism, which plays a key role in the adaptive plasticity of the DAergic system, sets the stage for some of the most critical interactions between cannabinoids and ATSs (which act as DA releasers)

clinical studies in animal models have enabled a preliminary characterization of the key domains of mutual interaction between cannabinoids and ATSs.

The stimulation of D_2 receptors (one of the key direct molecular effects of ATS) triggers anandamide synthesis in the striatum [219]; it appears that such process is teleologically directed at the attenuation of DA release and the reduction of DAergic psychomotor activation [219]. Notably, this mechanism may be contributed by TRPV1 receptors [220], which are abundantly expressed in DAergic neurons. In contrast, higher doses of cannabinoids (which are posited to stimulate CB_1 and CB_2 receptors across multiple sites) generally increase the activity of mesolimbic DAergic system including neuronal firing, DA release and metabolism and expression of D_1 receptors [221]. Accordingly, CB_1 receptor stimulation leads to the exacerbation of DA release in the nucleus accumbens induced by METH and AMPH [187, 222].

The bulk of evidence indicates that the endocannabinoid system is one of the main orchestrators of the plasticity of DAergic neurons [223–227]; accordingly, DA deficiency leads to a pronounced up-regulation of CB_1 receptors [228–230]. Based on these premises, it is possible that the interactions of ATSs and cannabinoids may be supported by mechanisms aimed at shaping short-term and long-term adaptive plasticity of the DAergic system.

These processes are likely to be regulated also by trace amines, and particularly β-PEA. This trace amine is likely to exert a modulatory role on DAergic plasticity through modifications of DA efflux modality in response to salient environmental inputs. Indeed, DA volume transmission may lead to differential patterns of activation of D_1 and D_2 receptors across the spines of medium-spiny neurons, the main population of output neurons in the striatum. The stimulation of these targets is in turn instrumental to the enactment of plasticity phenomena, such as long-term potentiation (LTP) and long-term depression (LTD). D_1 and D_2 receptors have differential roles in these two processes within the striatum: LTP is favored by D_1 receptor stimulation, but inhibited by D_2 receptor activation [231–233].

It is highly likely that ATSs may influence the synaptic plasticity of DAergic neurons by adopting mechanisms akin to those described above. For example, the repeated administration of ATSs leads to behavioral sensitization to the motoric responses induced by these drugs [234–236]. The stimulation of DA receptor, in turn, contributes to the synthesis of endocannabinoids, which shape plasticity processes through their action on GABAergic and glutamatergic neurons in close proximity with DAergic cells (see Chapt. 19 of this book). For example, the modulatory role of CB_1 receptors on the firing and activity of DAergic neurons is largely mediated by both glutamatergic and GABAergic neurons in the ventral tegmental area (VTA) of the midbrain, where they are abundantly expressed [237, 238].

On one hand, the GABAergic neurons of the VTA are posited to exert a tonic inhibition of DAergic neurons; thus, the activation of presynaptic CB_1 receptors leads to a reduction of GABA release, thereby increasing the activity of DAergic neurons [239, 240]. Physiologically, these CB_1 receptors are activated by 2-AG synthesized by the somatodendritic compartments of the DAergic neurons in the VTA. This phenomenon appears to be instrumental for habit formation [241] and may be essential for the enactment of responses to chronic ATS administration, such as sensitization to AMPH.

On the other hand, the initiation of sensitization to AMPH-induced hyperactivity is related to changes in glutamatergic transmission within the VTA [242], which lead to alterations in plasticity of the DAergic neurons in this area [243–247]. Indeed, the sensitization to AMPH is contributed by enhancements in glutamate receptor expression and increased responsiveness to glutamate in the synapses of the VTA, with a resulting suppression of LTD mechanisms [248–252]. This process is likely shaped by endocannabinoids. Although the mechanisms of this involvement are not completely clear, it is known that the cell bodies of DAergic neurons in the VTA auto-regulate their firing and bursting activity through the synthesis of 2-AG in response to metabotropic glutamate receptor stimulation [223]; the newly-synthesized 2-AG activates presynaptic CB_1 receptors by retrograde action, leading to the reduction of glutamate release [223].

Cannabinoids may also interact with ATSs by affecting D_1 and D_2 receptor responses in medium-spiny neurons. These interactions are based on the role of endocannabinoids as key modulators of DAergic neurotransmission in the basal ganglia [253–255]. Notably, CB_1 receptors are abundantly expressed in striatal neurons [256–259] and interact with both D_1 and D_2 receptors [260, 261]. Preliminary

evidence suggests that the combined activity of ATSs and cannabinoids may have differential effects on these two receptors. Accordingly, the transcripts of D_1 and D_2 receptors in striatum are respectively up-and down-regulated by the repeated treatment with METH and the anandamide analog methanandamide [262].

CB_1 receptor activation is posited to modulate the effects of striatal D_2 receptor signaling, as well as their effects on motor function [195, 219, 260, 263–265]. CB_1 receptors in the striatum are thought to condition the trafficking the D_2 receptors in response to activation [266]. The interaction of CB_1 and DAergic receptors is likely instrumental for the enactment of key plasticity processes, such as LTD and LTP. In the striatum, these mechanisms are actually influenced by both D_1 and D_2 receptors [235, 267–270]. The enactment of long-term plasticity at the striatal level is likely essential to shape the pattern of activation of this region in response to glutamatergic inputs from cortical neurons [271]. The effects of CB_1 receptors on D_1 and D_2 receptor signaling involve dopamine- and cAMP-regulated phosphoprotein of 32 kDa (DARPP-32) [265, 272], whose activation is also a fundamental requirement for LTD and LTP [273]. Furthermore, CB_1 and D_2 receptors are known to form heteromeric complexes, which, unlike the two individual receptors (which are coupled to G_I/G_o proteins), is coupled to a G_s protein [254, 274]. This suggests that the formation of these complexes can lead to significantly different phenotypical results than those produced by stimulation of each receptor [122].

One of the principal processes that may support the interactions of ATSs and cannabis with respect to the regulation of DAergic neurotransmission is LTD. This mechanism requires endocannabinoids in the striatum [224]. Several lines of evidence support the possibility that anandamide may be particularly implicated in this process. Indeed, this endocannabinoid has been shown to play an essential role in the developmental orchestration of LTD mechanisms [138]. Anandamide, but not 2-AG, is selectively produced by activation of D_2 receptors in striatum [219]. D_2 receptors have been shown to be necessary for LTD induction [232]. Notably, the implication of this anandamide in LTD is not limited to the striatum, but has also been attested in other brain regions, such as amygdala [275] and hippocampus [276]. In the latter region, it has been notably found that anandamide mediates LTD through activation of TRPV1, but not CB_1 receptors [276].

Indeed, it is interesting to note that some of the effects of cannabis may be mediated by TRPV1 receptors [277]. CBD and other ingredients of cannabis (such as cannabigerol, cannabigevarine and Δ9-Tetrahydrocannabinol) have been shown to activate these receptors [278–280]. Interestingly, Moreira and Guimarães [281] found that CBD countered the hyperlocomotive effects of AMPH, without inducing extrapyramidal-like effects. TRPV1 are activated by anandamide as well as N-arachidonoyl-dopamine (NADA), which is formed by DA linked to arachidonic acid by an amide bond, conferring properties of endocannabinoid and endovanilloid ligand [282]. This mechanism consists in the conjugation of arachidonic acid directly with DA [283]; while the role of this compound is not fully understood, recent evidence supports the possibility that it may be an antioxidant and exert neuroprotective properties [284]. Notably, anandamide has been shown to inhibit DAT through a mechanism not dependent on G-protein-coupled proteins [285], which may be related to the activation of TRPV1 receptors.

CB_2 receptors may be also implicated in the interactions of cannabis and ATSs. Accordingly, CB_2 receptors have been recently discovered in the brain and may play a role in certain mental disorders [124, 286]. The involvement of CB_2 receptors in the modulation of DAergic transmission is supported by the reduced expression of D_2 receptor in the prefrontal cortex of CB_2 knockout mice, as well as their enhanced responsiveness to cocaine [287]. Nevertheless, the involvement of CB_2 receptors in the outcomes of METH has been partially challenged by recent studies, finding the lack of implications of this receptor in the behavioral effects of METH [200].

Role of Cannabis in the Outcomes of METH Neurotoxicity

Another important theme of the potential combined role of cannabis and METH concerns the influence of cannabinoids on the neurotoxic sequelae induced by METH. In the striatum, METH neurotoxicity reflects deficits of DAergic, glutamatergic and GABAergic parvalbumin-positive neurons [288]; given the profound involvement of the endocannabinoid system in the regulation of GABA and glutamate signaling, it is expectable that METH neurotoxicity may be affected by cannabinoids and, in turn, alter the subjective responses to cannabis.

Although this important theme has been targeted by few clinical studies, a seminal contribution in this respect has been afforded by a study by Gonzalez and colleagues [289], who reported that heavy cannabis use did not exacerbate METH-induced cognitive impairments. On the contrary, users of both substances were found to display a milder severity of their neuropsychological deficits in comparison with users of METH alone, suggesting a protective role of cannabis against METH-induced abnormalities [289].

To verify the mutual interactions of cannabinoids and METH neurotoxicity, our group examined the effects of a "binge" schedule of METH (consisting in repeated administrations of high METH doses at short time intervals) on the expression and behavioral function of brain CB_1 receptors. METH neurotoxicity led to a significant increase of CB_1 receptor expression across key brain regions implicated in behavioral regulation (prefrontal cortex, striatum, amygdala and hippocampus) [216]. This up-regulation of CB_1 receptors following METH excitotoxicity is in line with previous evidence on similar phenomena consequent to neurotoxic insults [290, 291]. The bases of this phenomenon may be related to the well-characterized neuroprotective and anti-inflammatory actions of cannabinoids [292–296]. Thus, it is possible that the toxicity caused by ROSs may have stimulated CB_1 receptor upregulation as a countermeasure to curtail the deleterious impact of this drug. In addition, DA receptors may be involved in these phenomena. Interestingly, CB_1 receptor expression is increased by the lesion of DA terminals due to lesions [297]. Specifically, it is possible that the up-regulation of CB_1 receptors may limit glutamate efflux, which serves a key mediating role in METH-mediated neurotoxicity [117, 255].

The neuroprotective properties of cannabis may lie in the ability of THC to mimic the actions of 2-AG in inhibiting the release of glutamate by *depolarization-induced suppression of excitation* (DSE). Accordingly, CB_1 receptor agonists have been shown to reduce glutamate-mediated excitotoxicity in rodent brains [298–300]. Interestingly, both THC and CBD have been shown to have potent antioxidant properties [301, 302] and reduce the formation of ROSs. Cannabinoids have also been shown to reduce brain injury in ischemia models [292, 303–308], and may be therapeutically efficacious in the treatment of head trauma patients [309].

This background, together with the well-characterized neuroprotective and anti-inflammatory actions of CB_1 receptor agonists [292–296] highlights the possibility that CB_1 receptor synthesis may be stimulated by METH neurotoxicity in specific regions, as a countermeasure to curtail its deleterious impact. This may represent a compensatory mechanism to correct for the impaired GABA transmission.

Interestingly, the up-regulation of CB_1 receptors in METH-exposed rats were associated with an enhancement of anxiolytic properties of cannabinoids. This scenario suggests that METH neurotoxicity may result in altered responsiveness of CB_1 receptors, possibly due to selective damages of specific subpopulation of neurons and homeostatic imbalances of the endocannabinoid system in the brain areas that regulate the modality and intensity of environmental reactivity, such as amygdala, prefrontal cortex and hippocampus [106, 310].

Concluding Remarks

In this review, we have outlined the current knowledge and recent advances on the clinical and preclinical effects of cannabis and ATSs, a growing phenomenon that may have important negative repercussions particularly with respect to the development of psychotic disorders and addiction. We have also explored the mechanisms underlying these interactions, which represent the way for cannabinoids to interfere with the consequences of ATSs. As shown in the review, the interactions among these substances occur at multiple, highly integrated levels, reflecting a complex modulatory mechanism of endocannabinoids and dopamine, as well as other monoamines. Although the specific possibility of direct interactions between CB_1, TRPV1 and TAAR1 remains to be explored, it is likely that studies on these mechanisms may contribute to determine a number of pivotal discoveries in relation to the regulation of DA (also with respect to synaptic and extrasynaptic activation) and shed light on the neurobiological underpinnings of the psychiatric outcomes of the comorbid cannabis and ATS abuse.

Acknowledgments This chapter was partially supported by grants from the National Institute of Health (R21HD070611) and the Tourette Syndrome Association.

Glossary of Acronyms

2-AG	2-arachidonoylglycerol
5-HT	Serotonin
ADHD	Attention-deficit hyperactivity disorder
AMPH	d-amphetamine
ATSs	Amphetamine-type stimulants
CB1	Cannabinoid receptors type 1
CB2	Cannabinoid receptor type 2
CBD	Cannabidiol
CSF	Cerebrospinal fluid
DA	Dopamine
DARPP-32	Dopamine and cAMP-regulated phosphoprotein, 32 kDa
DAT	Dopamine transporter
DSE	Depolarization-induced suppression of excitation
FAAH	Fatty acid amide hydrolase
GABA	γ-aminobutyric acid
KO	Knockout
LTD	Long-term depression
LTP	Long-term potentiation
MAO	Monoamine oxidase
MDMA	3, 4-methylenedioxy-N-methylamphetamine
METH	Methamphetamine
NAPE	N-arachidonoyl phosphatidylethanolamine
NE	Norepinephrine
PKA	Protein kinases A
PKCΔ	Protein kinases C delta
ROSs	Reactive oxygen species
TAAR1	Trace amine associated receptor 1
THC	Δ9-tetrahydrocannabinol
TRPV1	Transient receptor potential cation channel subfamily V member 1
VMAT2	Vesicular monoamine transporter 2
VTA	Ventral tegmental area
β-PEA	β-phenylethylamine

References

1. Edeleano L. Ueber einige Derivate der Phenylmethacrylsäure und der Phenylisobuttersäure. Ber Dtsch Chem Ges. 1887;20:616–22.
2. Weisheit L, White RW. Methamphetamine: its history, pharmacology and treatment. Center City: Hazelden; 2009.
3. Abuse NIoD. NIDA Research Report Series: methamphetamine abuse and addiction. In: Rockville MD, editors. Dept. of Health and Human Services NIoH, National Institute on Drug Abuse. Research Report Series; 2002.

4. Anglin MD, Burke C, Perrochet B, Stamper E, Dawud-Noursi S. History of the methamphetamine problem. J Psychoactive Drugs. 2000;32(2):137–41.
5. D. S. Western Canadian Summit on methamphetamine: bringing together practitioners, policy makers and researchers: consensus panel report. Vancouver: Vancouver Coastal Health; 2005. p. 1–48.
6. Russell K, Dryden DM, Liang Y, Friesen C, O'Gorman K, Durec T, et al. Risk factors for methamphetamine use in youth: a systematic review. BMC Pediatr. 2008;8:48.
7. Iritani BJ, Hallfors DD, Bauer DJ. Crystal methamphetamine use among young adults in the USA. Addiction. 2007;102(7):1102–13.
8. Maxwell JC, Rutkowski BA. The prevalence of methamphetamine and amphetamine abuse in North America: a review of the indicators, 1992–2007. Drug Alcohol Rev. 2008;27(3):229–35.
9. McKetin R, Kozel N, Douglas J, Ali R, Vicknasingam B, Lund J, et al. The rise of methamphetamine in Southeast and East Asia. Drug Alcohol Rev. 2008;27(3):220–8.
10. United Nations, Publications. United Nations Office on Drugs and Crime: World Drug Report 2010. 2010.
11. Hollister L. Interactions of cannabis with other drugs in man. In: Ginzburg MCBHM, editor. Strategies for research on the interactions of drugs of abuse. Rockville: National Institute on Drug Abuse;1986.
12. Kalechstein AD, Newton TF, Longshore D, Anglin MD, van Gorp WG, Gawin FH. Psychiatric comorbidity of methamphetamine dependence in a forensic sample. J Neuropsychiatry Clin Neurosci. 2000;12(4):480–4.
13. Simon SL, Domier CP, Sim T, Richardson K, Rawson RA, Ling W. Cognitive performance of current methamphetamine and cocaine abusers. J Addict Dis. 2002;21(1):61–74.
14. Cottencin O, Rolland B, Karila L. New designer drugs (synthetic cannabinoids and synthetic cathinones): review of literature. Curr Pharm Des. 2014;20(25):4106–11.
15. Fisar Z. Phytocannabinoids and endocannabinoids. Curr Drug Abuse Rev. 2009;2(1):51–75.
16. Uchiyama N, Kawamura M, Kikura-Hanajiri R, Goda Y. URB-754: a new class of designer drug and 12 synthetic cannabinoids detected in illegal products. Forensic Sci Int. 2013;227(1–3):21–32.
17. Berry MD. Mammalian central nervous system trace amines. Pharmacologic amphetamines, physiologic neuromodulators. J Neurochem. 2004;90(2):257–71.
18. Bortolato M, Chen K, Shih JC. Monoamine oxidase inactivation: from pathophysiology to therapeutics. Adv Drug Deliv Rev. 2008;60(13–14):1527–33.
19. Paterson IA, Juorio AV, Boulton AA. 2-Phenylethylamine: a modulator of catecholamine transmission in the mammalian central nervous system? J Neurochem. 1990;55(6):1827–37.
20. Ishida K, Murata M, Katagiri N, Ishikawa M, Abe K, Kato M, et al. Effects of beta-phenylethylamine on dopaminergic neurons of the ventral tegmental area in the rat: a combined electrophysiological and microdialysis study. J Pharmacol Exp Ther. 2005;314(2):916–22.
21. Kuroki T, Tsutsumi T, Hirano M, Matsumoto T, Tatebayashi Y, Nishiyama K, et al. Behavioral sensitization to beta-phenylethylamine (PEA): enduring modifications of specific dopaminergic neuron systems in the rat. Psychopharmacology. 1990;102(1):5–10.
22. Sotnikova TD, Budygin EA, Jones SR, Dykstra LA, Caron MG, Gainetdinov RR. Dopamine transporter-dependent and -independent actions of trace amine beta-phenylethylamine. J Neurochem. 2004;91(2):362–73.
23. Ledonne A, Federici M, Giustizieri M, Pessia M, Imbrici P, Millan MJ, et al. Trace amines depress D(2)-autoreceptor-mediated responses on midbrain dopaminergic cells. Br J Pharmacol. 2010;160(6):1509–20.
24. Borowsky B, Adham N, Jones KA, Raddatz R, Artymyshyn R, Ogozalek KL, et al. Trace amines: identification of a family of mammalian G protein-coupled receptors. Proc Nat Acad Sci U S A. 2001;98(16):8966–71.
25. Miller GM, Verrico CD, Jassen A, Konar M, Yang H, Panas H, et al. Primate trace amine receptor 1 modulation by the dopamine transporter. J Pharmacol Exp Ther. 2005;313(3):983–94.

26. Xie Z, Westmoreland SV, Miller GM. Modulation of monoamine transporters by common biogenic amines via trace amine-associated receptor 1 and monoamine autoreceptors in human embryonic kidney 293 cells and brain synaptosomes. J Pharmacol Exp Ther. 2008;325(2):629–40.
27. Xie Z, Miller GM. Trace amine-associated receptor 1 is a modulator of the dopamine transporter. J Pharmacol Exp Ther. 2007;321(1):128–36.
28. Rothman RB, Baumann MH. Monoamine transporters and psychostimulant drugs. Eur J Pharmacol. 2003;479(1–3):23–40.
29. Han DD, Gu HH. Comparison of the monoamine transporters from human and mouse in their sensitivities to psychostimulant drugs. BMC Pharmacol. 2006;6:6.
30. Eshleman AJ, Henningsen RA, Neve KA, Janowsky A. Release of dopamine via the human transporter. Mol Pharmacol. 1994;45(2):312–6.
31. Sitte HH, Huck S, Reither H, Boehm S, Singer EA, Pifl C. Carrier-mediated release, transport rates, and charge transfer induced by amphetamine, tyramine, and dopamine in mammalian cells transfected with the human dopamine transporter. J Neurochem. 1998;71(3):1289–97.
32. Jones SR, Gainetdinov RR, Wightman RM, Caron MG. Mechanisms of amphetamine action revealed in mice lacking the dopamine transporter. J Neurosci. 1998;18(6):1979–86.
33. Bunzow JR, Sonders MS, Arttamangkul S, Harrison LM, Zhang G, Quigley DI, et al. Amphetamine, 3,4-methylenedioxymethamphetamine, lysergic acid diethylamide, and metabolites of the catecholamine neurotransmitters are agonists of a rat trace amine receptor. Mol Pharmacol. 2001;60(6):1181–8.
34. Fleckenstein AE, Metzger RR, Gibb JW, Hanson GR. A rapid and reversible change in dopamine transporters induced by methamphetamine. Eur J Pharmacol. 1997;323(2–3):R9–10.
35. Xie Z, Westmoreland SV, Bahn ME, Chen GL, Yang H, Vallender EJ, et al. Rhesus monkey trace amine-associated receptor 1 signaling: enhancement by monoamine transporters and attenuation by the D2 autoreceptor in vitro. J Pharmacol Exp Ther. 2007;321(1):116–27.
36. Shin EJ, Duong CX, Nguyen XK, Li Z, Bing G, Bach JH, et al. Role of oxidative stress in methamphetamine-induced dopaminergic toxicity mediated by protein kinase Cdelta. Behav Brain Res. 2012;232(1):98–113.
37. Sandoval V, Riddle EL, Ugarte YV, Hanson GR, Fleckenstein AE. Methamphetamine-induced rapid and reversible changes in dopamine transporter function: an in vitro model. J Neurosci. 2001;21(4):1413–9.
38. Lindemann L, Meyer CA, Jeanneau K, Bradaia A, Ozmen L, Bluethmann H, et al. Trace amine-associated receptor 1 modulates dopaminergic activity. J Pharmacol Exp Ther. 2008;324(3):948–56.
39. Erickson JD, Schafer MK, Bonner TI, Eiden LE, Weihe E. Distinct pharmacological properties and distribution in neurons and endocrine cells of two isoforms of the human vesicular monoamine transporter. Proc Natl Acad Sci U S A. 1996;93(10):5166–71.
40. Nickell JR, Krishnamurthy S, Norrholm S, Deaciuc G, Siripurapu KB, Zheng G, et al. Lobelane inhibits methamphetamine-evoked dopamine release via inhibition of the vesicular monoamine transporter-2. J Pharmacol Exp Ther. 2010;332(2):612–21.
41. Horton DB, Siripurapu KB, Norrholm SD, Culver JP, Hojahmat M, Beckmann JS, et al. meso-Transdiene analogs inhibit vesicular monoamine transporter-2 function and methamphetamine-evoked dopamine release. J Pharmacol Exp Ther. 2011;336(3):940–51.
42. Alvers KM, Beckmann JS, Zheng G, Crooks PA, Dwoskin LP, Bardo MT. The effect of VMAT2 inhibitor GZ-793 A on the reinstatement of methamphetamine-seeking in rats. Psychopharmacology. 2012;224(2):255–62.
43. Fumagalli F, Gainetdinov RR, Wang YM, Valenzano KJ, Miller GW, Caron MG. Increased methamphetamine neurotoxicity in heterozygous vesicular monoamine transporter 2 knockout mice. J Neurosci. 1999;19(7):2424–31.
44. Takahashi N, Miner LL, Sora I, Ujike H, Revay RS, Kostic V, et al. VMAT2 knockout mice: heterozygotes display reduced amphetamine-conditioned reward, enhanced amphetamine locomotion, and enhanced MPTP toxicity. Proc Natl Acad Sci U S A. 1997;94(18):9938–43.

45. Wang YM, Gainetdinov RR, Fumagalli F, Xu F, Jones SR, Bock CB, et al. Knockout of the vesicular monoamine transporter 2 gene results in neonatal death and supersensitivity to cocaine and amphetamine. Neuron. 1997;19(6):1285–96.
46. Miller HH, Shore PA, Clarke DE. In vivo monoamine oxidase inhibition by d-amphetamine. Biochemical Pharmacol. 1980;29(10):1347–54.
47. Kita T, Philbert MA, Wagner GC, Huang J, Lowndes HE. Methamphetamine-induced modification of dopamine metabolism in cultured striatal astrocytes. Pharmacol Toxicol. 1998;83(1):36–9.
48. Descarries L, Watkins KC, Garcia S, Bosler O, Doucet G. Dual character, asynaptic and synaptic, of the dopamine innervation in adult rat neostriatum: a quantitative autoradiographic and immunocytochemical analysis. J Comp Neurol. 1996;375(2):167–86.
49. Descarries L, Mechawar N. Ultrastructural evidence for diffuse transmission by monoamine and acetylcholine neurons of the central nervous system. Prog Brain Res. 2000;125:27–47.
50. Fuxe K, Dahlstrom A, Hoistad M, Marcellino D, Jansson A, Rivera A, et al. From the Golgi-Cajal mapping to the transmitter-based characterization of the neuronal networks leading to two modes of brain communication: wiring and volume transmission. Brain Res Rev. 2007;55(1):17–54.
51. Zoli M, Agnati LF. Wiring and volume transmission in the central nervous system: the concept of closed and open synapses. Prog Neurobiol. 1996;49(4):363–80.
52. Murray RM, Lappin J, Di Forti M. Schizophrenia: from developmental deviance to dopamine dysregulation. Eur Neuropsychopharmacol. 2008;18 Suppl 3:129–34.
53. Braff DL, Geyer MA. Sensorimotor gating and schizophrenia. Human and animal model studies. Arch Gen Psychiatry. 1990;47(2):181–8.
54. Swerdlow NR, Stephany N, Wasserman LC, Talledo J, Shoemaker J, Auerbach PP. Amphetamine effects on prepulse inhibition across-species: replication and parametric extension. Neuropsychopharmacology. 2003;28(4):640–50.
55. Chou YH, Karlsson P, Halldin C, Olsson H, Farde L. A PET study of D(1)-like dopamine receptor ligand binding during altered endogenous dopamine levels in the primate brain. Psychopharmacology. 1999;146(2):220–7.
56. Bergson C, Mrzljak L, Smiley JF, Pappy M, Levenson R, Goldman-Rakic PS. Regional, cellular, and subcellular variations in the distribution of D1 and D5 dopamine receptors in primate brain. J Neurosci. 1995;15(12):7821–36.
57. Yung KK, Bolam JP, Smith AD, Hersch SM, Ciliax BJ, Levey AI. Immunocytochemical localization of D1 and D2 dopamine receptors in the basal ganglia of the rat: light and electron microscopy. Neuroscience. 1995;65(3):709–30.
58. Sesack SR, Aoki C, Pickel VM. Ultrastructural localization of D2 receptor-like immunoreactivity in midbrain dopamine neurons and their striatal targets. J Neurosci. 1994;14(1):88–106.
59. Tirotta E DMC, Iitaka C, Ramos M, Holmes D, Borrelli E. U. Unraveling the role of dopamine receptors in vivo: lessons from knockout mice. In: KA N. The dopamine receptors. 2 ed. New York: Humana; 2010. p. 303–22.
60. Marcellino D, Kehr J, Agnati LF, Fuxe K. Increased affinity of dopamine for D(2)-like versus D(1) -like receptors. Relevance for volume transmission in interpreting PET findings. Synapse. 2012;66(3):196–203.
61. Rolinski Z, Scheel-Kruger J. The effect of dopamine and noradrenaline antagonists on amphetamine induced locomotor activity in mice and rats. Acta Pharmacol Toxicol. 1973;33(5):385–99.
62. Paulus MP, Geyer MA. A scaling approach to find order parameters quantifying the effects of dopaminergic agents on unconditioned motor activity in rats. Prog Neuropsychopharmacol Biol Psychiatry.1991;15(6):903–19.
63. Lapin IP, Rogawski MA. Effects of D1 and D2 dopamine receptor antagonists and catecholamine depleting agents on the locomotor stimulation induced by dizocilpine in mice. Behav Brain Res. 1995;70(2):145–51.

64. O'Neill MF, Shaw G. Comparison of dopamine receptor antagonists on hyperlocomotion induced by cocaine, amphetamine, MK-801 and the dopamine D1 agonist C-APB in mice. Psychopharmacology. 1999;145(3):237–50.
65. Ralph RJ, Varty GB, Kelly MA, Wang YM, Caron MG, Rubinstein M, et al. The dopamine D2, but not D3 or D4, receptor subtype is essential for the disruption of prepulse inhibition produced by amphetamine in mice. J Neurosci. 1999;19(11):4627–33.
66. Kim SE, Han SM. Nicotine- and methamphetamine-induced dopamine release evaluated with in-vivo binding of radiolabelled raclopride to dopamine D2 receptors: comparison with in-vivo microdialysis data. Int J Neuropsychopharmacol. 2009;12(6):833–41.
67. Gonon F. Prolonged and extrasynaptic excitatory action of dopamine mediated by D1 receptors in the rat striatum in vivo. J Neurosci. 1997;17(15):5972–8.
68. Centonze D, Picconi B, Baunez C, Borrelli E, Pisani A, Bernardi G, et al. Cocaine and amphetamine depress striatal GABAergic synaptic transmission through D2 dopamine receptors. Neuropsychopharmacology. 2002;26(2):164–75.
69. Cepeda C, Hurst RS, Altemus KL, Flores-Hernandez J, Calvert CR, Jokel ES, et al. Facilitated glutamatergic transmission in the striatum of D2 dopamine receptor-deficient mice. J Neurophysiol. 2001;85(2):659–70.
70. Chesselet MF, Plotkin JL, Wu N, Levine MS. Development of striatal fast-spiking GABAergic interneurons. Prog Brain Res. 2007;160:261–72.
71. Bamford NS, Zhang H, Schmitz Y, Wu NP, Cepeda C, Levine MS, et al. Heterosynaptic dopamine neurotransmission selects sets of corticostriatal terminals. Neuron. 2004;42(4):653–63.
72. Jones S, Kauer JA. Amphetamine depresses excitatory synaptic transmission via serotonin receptors in the ventral tegmental area. J Neurosci. 1999;19(22):9780–7.
73. Rothman RB, Baumann MH, Dersch CM, Romero DV, Rice KC, Carroll FI, et al. Amphetamine-type central nervous system stimulants release norepinephrine more potently than they release dopamine and serotonin. Synapse. 2001;39(1):32–41.
74. Ventura R, Cabib S, Alcaro A, Orsini C, Puglisi-Allegra S. Norepinephrine in the prefrontal cortex is critical for amphetamine-induced reward and mesoaccumbens dopamine release. J Neurosci. 2003;23(5):1879–85.
75. Del Arco A Martinez R Mora F. Amphetamine increases extracellular concentrations of glutamate in the prefrontal cortex of the awake rat: a microdialysis study. Neurochem Res. 1998;23(9):1153–8.
76. Miele M, Mura MA, Enrico P, Esposito G, Serra PA, Migheli R, et al. On the mechanism of d-amphetamine-induced changes in glutamate, ascorbic acid and uric acid release in the striatum of freely moving rats. Br J Pharmacol. 2000;129(3):582–8.
77. Paladini CA, Fiorillo CD, Morikawa H, Williams JT. Amphetamine selectively blocks inhibitory glutamate transmission in dopamine neurons. Nat Neurosci. 2001;4(3):275–81.
78. Ernst T, Chang L, Leonido-Yee M, Speck O. Evidence for long-term neurotoxicity associated with methamphetamine abuse: a 1H MRS study. Neurology. 2000;54(6):1344–9.
79. Volkow ND, Chang L, Wang GJ, Fowler JS, Ding YS, Sedler M, et al. Low level of brain dopamine D2 receptors in methamphetamine abusers: association with metabolism in the orbitofrontal cortex. Am J Psychiatry. 2001;158(12):2015–21.
80. Cubells JF, Rayport S, Rajendran G, Sulzer D. Methamphetamine neurotoxicity involves vacuolation of endocytic organelles and dopamine-dependent intracellular oxidative stress. J Neurosci. 1994;14(4):2260–71.
81. Larsen KE, Fon EA, Hastings TG, Edwards RH, Sulzer D. Methamphetamine-induced degeneration of dopaminergic neurons involves autophagy and upregulation of dopamine synthesis. J Neurosci. 2002;22(20):8951–60.
82. Cadet JL, Sheng P, Ali S, Rothman R, Carlson E, Epstein C. Attenuation of methamphetamine-induced neurotoxicity in copper/zinc superoxide dismutase transgenic mice. J Neurochem. 1994;62(1):380–3.
83. Hirata H, Ladenheim B, Rothman RB, Epstein C, Cadet JL. Methamphetamine-induced serotonin neurotoxicity is mediated by superoxide radicals. Brain Res. 1995;677(2):345–7.

84. Yamamoto BK, Zhu W. The effects of methamphetamine on the production of free radicals and oxidative stress. J Pharmacol Exp Ther. 1998;287(1):107–14.
85. Perfeito R, Cunha-Oliveira T, Rego AC. Reprint of: revisiting oxidative stress and mitochondrial dysfunction in the pathogenesis of Parkinson disease-resemblance to the effect of amphetamine drugs of abuse. Free Radic Biol Med. 2013;62:186–201.
86. Kiyatkin EA, Sharma HS. Acute methamphetamine intoxication: brain hyperthermia, blood-brain barrier, brain edema, and morphological cell abnormalities. Int Rev Neurobiol. 2009;88:65–100.
87. Bowyer JF, Davies DL, Schmued L, Broening HW, Newport GD, Slikker W, Jr., et al. Further studies of the role of hyperthermia in methamphetamine neurotoxicity. J Pharmacol Exp Ther. 1994;268(3):1571–80.
88. Davidson C, Gow AJ, Lee TH, Ellinwood EH. Methamphetamine neurotoxicity: necrotic and apoptotic mechanisms and relevance to human abuse and treatment. Brain Res Brain Res Rev. 2001;36(1):1–22.
89. Vergo S, Johansen JL, Leist M, Lotharius J. Vesicular monoamine transporter 2 regulates the sensitivity of rat dopaminergic neurons to disturbed cytosolic dopamine levels. Brain Res. 2007;1185:18–32.
90. Guillot TS, Shepherd KR, Richardson JR, Wang MZ, Li Y, Emson PC, et al. Reduced vesicular storage of dopamine exacerbates methamphetamine-induced neurodegeneration and astrogliosis. J Neurochem. 2008;106(5):2205–17.
91. Hadlock GC, Chu PW, Walters ET, Hanson GR, Fleckenstein AE. Methamphetamine-induced dopamine transporter complex formation and dopaminergic deficits: the role of D2 receptor activation. J Pharmacol Exp Ther. 2010;335(1):207–12.
92. Mark KA, Soghomonian JJ, Yamamoto BK. High-dose methamphetamine acutely activates the striatonigral pathway to increase striatal glutamate and mediate long-term dopamine toxicity. J Neurosci. 2004;24(50):11449–56.
93. Sonsalla PK, Nicklas WJ, Heikkila RE. Role for excitatory amino acids in methamphetamine-induced nigrostriatal dopaminergic toxicity. Science. 1989;243(4889):398–400.
94. Deng X, Cadet JL. Methamphetamine-induced apoptosis is attenuated in the striata of copper-zinc superoxide dismutase transgenic mice. Brain Res Mol Brain Res. 2000;83(1–2):121–4.
95. Deng X, Cai NS, McCoy MT, Chen W, Trush MA, Cadet JL. Methamphetamine induces apoptosis in an immortalized rat striatal cell line by activating the mitochondrial cell death pathway. Neuropharmacology. 2002;42(6):837–45.
96. Cadet JL, Krasnova IN, Jayanthi S, Lyles J. Neurotoxicity of substituted amphetamines: molecular and cellular mechanisms. Neurotox Res. 2007;11(3–4):183–202.
97. Hall W, Solowij N. Adverse effects of cannabis. Lancet. 1998;352(9140):1611–6.
98. Salo R, Nordahl TE, Natsuaki Y, Leamon MH, Galloway GP, Waters C, et al. Attentional control and brain metabolite levels in methamphetamine abusers. Biol Psychiatry. 2007;61(11):1272–80.
99. Degenhardt L, Hall W. Is cannabis use a contributory cause of psychosis? Can J Psychiatry. 2006;51(9):556–65.
100. Callaghan RC, Cunningham JK, Allebeck P, Arenovich T, Sajeev G, Remington G, et al. Methamphetamine use and schizophrenia: a population-based cohort study in California. Am J Psychiatry. 2012;169(4):389–96.
101. Arseneault L, Moffit TE, Caspi A, Taylor A. The targets of violence committed by young offenders with alcohol dependence, marijuana dependence and schizophrenia-spectrum disorders: findings from a birth cohort. Crim Behav Ment Health. 2002;12(2):155–68.
102. Henquet C, Krabbendam L, Spauwen J, Kaplan C, Lieb R, Wittchen HU, et al. Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people. BMJ. 2005;330(7481):11.
103. Evans MA, Martz R, Rodda BE, Lemberger L, Forney RB. Effects of marihuana-dextroamphetamine combination. Clin Pharmacol Ther. 1976;20(3):350–8.
104. Foltin RW, Fischman MW, Pippen PA, Kelly TH. Behavioral effects of cocaine alone and in combination with ethanol or marijuana in humans. Drug Alcohol Depend. 1993;32(2):93–106.

105. Hayase T, Yamamoto Y, Yamamoto K. Persistent anxiogenic effects of a single or repeated doses of cocaine and methamphetamine: interactions with endogenous cannabinoid receptor ligands. Behav Pharmacol. 2005;16(5–6):395–404.
106. Tambaro S, Bortolato M. Cannabinoid-related agents in the treatment of anxiety disorders: current knowledge and future perspectives. Recent Pat CNS Drug Discov. 2012;7(1):25–40.
107. Fowler JS, Volkow ND, Logan J, Alexoff D, Telang F, Wang GJ, et al. Fast uptake and long-lasting binding of methamphetamine in the human brain: comparison with cocaine. Neuroimage. 2008;43(4):756–63.
108. De Petrocellis L Cascio MG Di Marzo V. The endocannabinoid system: a general view and latest additions. Br J Pharmacol. 2004;141(5):765–74.
109. Mechoulam R, Parker LA. The endocannabinoid system and the brain. Annu Rev Psychol. 2013;64:21–47.
110. Howlett AC, Qualy JM, Khachatrian LL. Involvement of Gi in the inhibition of adenylate cyclase by cannabimimetic drugs. Mol Pharmacol. 1986;29(3):307–13.
111. Matsuda LA, Lolait SJ, Brownstein MJ, Young AC, Bonner TI. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. Nature. 1990;346(6284):561–4.
112. Munro S, Thomas KL, Abu-Shaar M. Molecular characterization of a peripheral receptor for cannabinoids. Nature. 1993;365(6441):61–5.
113. Freund TF, Katona I, Piomelli D. Role of endogenous cannabinoids in synaptic signaling. Physiol Rev. 2003;83(3):1017–66.
114. Mackie K. Distribution of cannabinoid receptors in the central and peripheral nervous system. Handb Exp Pharmacol. 2005;168:299–325.
115. Morishita W, Alger BE. Evidence for endogenous excitatory amino acids as mediators in DSI of GABA(A)ergic transmission in hippocampal CA1. J Neurophysiol. 1999;82(5):2556–64.
116. Wilson RI, Nicoll RA. Endogenous cannabinoids mediate retrograde signalling at hippocampal synapses. Nature. 2001;410(6828):588–92.
117. Ohno-Shosaku T, Maejima T, Kano M. Endogenous cannabinoids mediate retrograde signals from depolarized postsynaptic neurons to presynaptic terminals. Neuron. 2001;29(3):729–38.
118. Varma N, Carlson GC, Ledent C, Alger BE. Metabotropic glutamate receptors drive the endocannabinoid system in hippocampus. J Neurosci. 2001;21(24):RC188.
119. Lovinger DM. Presynaptic modulation by endocannabinoids. Handb Exp Pharmacol. 2008;184:435–77.
120. Pertwee RG, Howlett AC, Abood ME, Alexander SP, Di Marzo V, Elphick MR, et al. International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB(1) and CB(2). Pharmacol Rev. 2010;62(4):588–631.
121. Hudson BD, Hebert TE, Kelly ME. Ligand- and heterodimer-directed signaling of the CB(1) cannabinoid receptor. Mol Pharmacol. 2010;77(1):1–9.
122. Ferre S, Goldberg SR, Lluis C, Franco R. Looking for the role of cannabinoid receptor heteromers in striatal function. Neuropharmacology. 2009;56 Suppl 1:226–34.
123. Walter L, Stella N. Cannabinoids and neuroinflammation. Br J Pharmacol. 2004;141(5):775–85.
124. Van Sickle MD, Duncan M, Kingsley PJ, Mouihate A, Urbani P, Mackie K, et al. Identification and functional characterization of brainstem cannabinoid CB2 receptors. Science. 2005;310(5746):329–32.
125. Gong JP, Onaivi ES, Ishiguro H, Liu QR, Tagliaferro PA, Brusco A, et al. Cannabinoid CB2 receptors: immunohistochemical localization in rat brain. Brain Res. 2006;1071(1):10–23.
126. Mechoulam R, Ben-Shabat S, Hanus L, Ligumsky M, Kaminski NE, Schatz AR, et al. Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. Biochem Pharmacol. 1995;50(1):83–90.
127. Sugiura T, Kondo S, Sukagawa A, Nakane S, Shinoda A, Itoh K, et al. 2-Arachidonoylglycerol: a possible endogenous cannabinoid receptor ligand in brain. Biochem Biophys Res Commun. 1995;215(1):89–97.

128. Devane WA, Hanus L, Breuer A, Pertwee RG, Stevenson LA, Griffin G, et al. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. Science. 1992;258(5090):1946–9.
129. Okamoto Y, Morishita J, Tsuboi K, Tonai T, Ueda N. Molecular characterization of a phospholipase D generating anandamide and its congeners. J Biol Chem. 2004;279(7):5298–305.
130. Sun YX, Tsuboi K, Okamoto Y, Tonai T, Murakami M, Kudo I, et al. Biosynthesis of anandamide and N-palmitoylethanolamine by sequential actions of phospholipase A2 and lysophospholipase D. Biochem J. 2004;380(Pt 3):749–56.
131. Di Marzo V, Fontana A, Cadas H, Schinelli S, Cimino G, Schwartz JC, et al. Formation and inactivation of endogenous cannabinoid anandamide in central neurons. Nature. 1994;372(6507):686–91.
132. Beltramo M, Stella N, Calignano A, Lin SY, Makriyannis A, Piomelli D. Functional role of high-affinity anandamide transport, as revealed by selective inhibition. Science. 1997;277(5329):1094–7.
133. Hillard CJ, Campbell WB. Biochemistry and pharmacology of arachidonylethanolamide, a putative endogenous cannabinoid. J Lipid Res. 1997;38(12):2383–98.
134. Fegley D, Kathuria S, Mercier R, Li C, Goutopoulos A, Makriyannis A, et al. Anandamide transport is independent of fatty-acid amide hydrolase activity and is blocked by the hydrolysis-resistant inhibitor AM1172. Proc Natl Acad Sci U S A. 2004;101(23):8756–61.
135. Hillard CJ, Wilkison DM, Edgemond WS, Campbell WB. Characterization of the kinetics and distribution of N-arachidonylethanolamine (anandamide) hydrolysis by rat brain. Biochim Biophys Acta. 1995;1257(3):249–56.
136. Ueda N, Kurahashi Y, Yamamoto S, Tokunaga T. Partial purification and characterization of the porcine brain enzyme hydrolyzing and synthesizing anandamide. J Biol Chem. 1995;270(40):23823–7.
137. Cravatt BF, Giang DK, Mayfield SP, Boger DL, Lerner RA, Gilula NB. Molecular characterization of an enzyme that degrades neuromodulatory fatty-acid amides. Nature. 1996;384(6604):83–7.
138. Ade KK, Lovinger DM. Anandamide regulates postnatal development of long-term synaptic plasticity in the rat dorsolateral striatum. J Neurosci. 2007;27(9):2403–9.
139. Maccarrone M, Rossi S, Bari M, De Chiara V, Fezza F, Musella A, et al. Anandamide inhibits metabolism and physiological actions of 2-arachidonoylglycerol in the striatum. Nat Neurosci. 2008;11(2):152–9.
140. Maccarrone M, De Chiara V, Gasperi V, Viscomi MT, Rossi S, Oddi S, et al. Lipid rafts regulate 2-arachidonoylglycerol metabolism and physiological activity in the striatum. J Neurochem. 2009;109(2):371–81.
141. Rossi S, De Chiara V, Musella A, Sacchetti L, Cantarella C, Castelli M, et al. Preservation of striatal cannabinoid CB1 receptor function correlates with the antianxiety effects of fatty acid amide hydrolase inhibition. Mol Pharmacol. 2010;78(2):260–8.
142. Power BD, Stefanis NC, Dragovic M, Jablensky A, Castle D, Morgan V. Age at initiation of amphetamine use and age at onset of psychosis: the Australian Survey of High Impact Psychosis. Schizophr Res. 2014;152(1):300–2.
143. Muller-Vahl KR, Emrich HM. Cannabis and schizophrenia: towards a cannabinoid hypothesis of schizophrenia. Expert Rev Neurother. 2008;8(7):1037–48.
144. Giuffrida A, Leweke FM, Gerth CW, Schreiber D, Koethe D, Faulhaber J, et al. Cerebrospinal anandamide levels are elevated in acute schizophrenia and are inversely correlated with psychotic symptoms. Neuropsychopharmacology. 2004;29(11):2108–14.
145. Parolaro D, Realini N, Vigano D, Guidali C, Rubino T. The endocannabinoid system and psychiatric disorders. Exp Neurol. 2010;224(1):3–14.
146. De Marchi N De Petrocellis L Orlando P Daniele F Fezza F Di Marzo V. Endocannabinoid signalling in the blood of patients with schizophrenia. Lipids Health Dis. 2003;2:5.
147. Dean B, Sundram S, Bradbury R, Scarr E, Copolov D. Studies on [3H]CP-55940 binding in the human central nervous system: regional specific changes in density of cannabinoid-1

receptors associated with schizophrenia and cannabis use. Neuroscience. 2001;103(1):9–15.
148. Zavitsanou K, Garrick T, Huang XF. Selective antagonist [3H]SR141716 A binding to cannabinoid CB1 receptors is increased in the anterior cingulate cortex in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2004;28(2):355–60.
149. Newell KA, Deng C, Huang XF. Increased cannabinoid receptor density in the posterior cingulate cortex in schizophrenia. Exp Brain Res. 2006;172(4):556–60.
150. Uriguen L, Garcia-Fuster MJ, Callado LF, Morentin B, La Harpe R, Casado V, et al. Immunodensity and mRNA expression of A2 A adenosine, D2 dopamine, and CB1 cannabinoid receptors in postmortem frontal cortex of subjects with schizophrenia: effect of antipsychotic treatment. Psychopharmacology. 2009;206(2):313–24.
151. Broome MR, Woolley JB, Tabraham P, Johns LC, Bramon E, Murray GK, et al. What causes the onset of psychosis? Schizophr Res. 2005 ;79(1):23–34.
152. Iyo M, Sekine Y, Mori N. Neuromechanism of developing methamphetamine psychosis: a neuroimaging study. Ann N Y Acad Sci. 2004;1025:288–95.
153. Ujike H, Katsu T, Okahisa Y, Takaki M, Kodama M, Inada T, et al. Genetic variants of D2 but not D3 or D4 dopamine receptor gene are associated with rapid onset and poor prognosis of methamphetamine psychosis. Prog Neuropsychopharmacol Biol Psychiatry. 2009;33(4):625–9.
154. Voruganti LN, Slomka P, Zabel P, Mattar A, Awad AG. Cannabis induced dopamine release: an in-vivo SPECT study. Psychiatry Res. 2001;107(3):173–7.
155. Bossong MG, van Berckel BN, Boellaard R, Zuurman L, Schuit RC, Windhorst AD, et al. Delta9-tetrahydrocannabinol induces dopamine release in the human striatum. Neuropsychopharmacology. 2009;34(3):759–66.
156. Stokes PR, Mehta MA, Curran HV, Breen G, Grasby PM. Can recreational doses of THC produce significant dopamine release in the human striatum? NeuroImage. 2009;48(1):186–90.
157 D'Souza DC, Sewell RA, Ranganathan M. Cannabis and psychosis/schizophrenia: human studies. Eur Arch Psychiatry Clin Neurosci. 2009;259(7):413–31.
158. Okahisa Y, Kodama M, Takaki M, Inada T, Uchimura N, Yamada M, et al. Association Study of Two Cannabinoid Receptor Genes, CNR1 and CNR2, with Methamphetamine Dependence. Curr Neuropharmacol. 2011;9(1):183–9.
159. Ujike H, Takaki M, Nakata K, Tanaka Y, Takeda T, Kodama M, et al. CNR1, central cannabinoid receptor gene, associated with susceptibility to hebephrenic schizophrenia. Molecular Psychiatry. 2002;7(5):515–8.
160. Martinez-Gras I, Hoenicka J, Ponce G, Rodriguez-Jimenez R, Jimenez-Arriero MA, Perez-Hernandez E, et al. (AAT)n repeat in the cannabinoid receptor gene, CNR1: association with schizophrenia in a Spanish population. Eur Arch Psychiatry Clin Neurosci. 2006;256(7):437–41.
161. Ballmaier M, Bortolato M, Rizzetti C, Zoli M, Gessa G, Heinz A, et al. Cannabinoid receptor antagonists counteract sensorimotor gating deficits in the phencyclidine model of psychosis. Neuropsychopharmacology. 2007;32(10):2098–107.
162. Tzavara ET, Degroot A, Wade MR, Davis RJ, Nomikos GG. CB1 receptor knockout mice are hyporesponsive to the behavior-stimulating actions of d-amphetamine: role of mGlu5 receptors. Eur Neuropsychopharmacol. 2009;19(3):196–204.
163. Meltzer HY, Arvanitis L, Bauer D, Rein W, Meta-Trial Study G. Placebo-controlled evaluation of four novel compounds for the treatment of schizophrenia and schizoaffective disorder. Am J Psychiatry. 2004;161(6):975–84.
164. Fergusson DM, Horwood LJ. Does cannabis use encourage other forms of illicit drug use? Addiction. 2000 Apr;95(4):505–20.
165. Morral AR, McCaffrey DF, Paddock SM. Reassessing the marijuana gateway effect. Addiction. 2002;97(12):1493–504.
166. Hall WD, Lynskey M. Is cannabis a gateway drug? Testing hypotheses about the relationship between cannabis use and the use of other illicit drugs. Drug Alcohol Rev. 2005;24(1):39–48.

167. Molitor F, Ruiz JD, Flynn N, Mikanda JN, Sun RK, Anderson R. Methamphetamine use and sexual and injection risk behaviors among out-of-treatment injection drug users. Am J Drug Alcohol Abuse. 1999;25(3):475–93.
168. Baskin-Sommers A, Sommers I. The co-occurrence of substance use and high-risk behaviors. J Adolesc Health. 2006;38(5):609–11.
169. Scott LA, Roxburgh A, Bruno R, Matthews A, Burns L. The impact of comorbid cannabis and methamphetamine use on mental health among regular ecstasy users. Addict Behav. 2012;37(9):1058–62.
170. Churchwell JC, Carey PD, Ferrett HL, Stein DJ, Yurgelun-Todd DA. Abnormal striatal circuitry and intensified novelty seeking among adolescents who abuse methamphetamine and cannabis. Dev Neurosci. 2012;34(4):310–7.
171. Oliere S, Joliette-Riopel A, Potvin S, Jutras-Aswad D. Modulation of the endocannabinoid system: vulnerability factor and new treatment target for stimulant addiction. Front Psychiatry. 2013;4:109.
172. Dlugos AM, Hamidovic A, Hodgkinson CA, Goldman D, Palmer AA, de Wit H. More aroused, less fatigued: fatty acid amide hydrolase gene polymorphisms influence acute response to amphetamine. Neuropsychopharmacology. 2010;35(3):613–22.
173. Sipe JC, Chiang K, Gerber AL, Beutler E, Cravatt BF. A missense mutation in human fatty acid amide hydrolase associated with problem drug use. Proc Natl Acad Sci U S A. 2002;99(12):8394–9.
174. Morita Y, Ujike H, Tanaka Y, Uchida N, Nomura A, Ohtani K, et al. A nonsynonymous polymorphism in the human fatty acid amide hydrolase gene did not associate with either methamphetamine dependence or schizophrenia. Neurosci Lett. 2005;376(3):182–7.
175. Comings DE, Muhleman D, Gade R, Johnson P, Verde R, Saucier G, et al. Cannabinoid receptor gene (CNR1): association with i.v. drug use. Mol Psychiatry. 1997;2(2):161–8.
176. Zhang PW, Ishiguro H, Ohtsuki T, Hess J, Carillo F, Walther D, et al. Human cannabinoid receptor 1: 5' exons, candidate regulatory regions, polymorphisms, haplotypes and association with polysubstance abuse. Mol Psychiatry. 2004;9(10):916–31.
177. Madsen MV, Peacock L, Werge T, Andersen MB. Effects of the cannabinoid CB1 receptor agonist CP55,940 and antagonist SR141716 A on d-amphetamine-induced behaviours in Cebus monkeys. J Psychopharmacol. 2006;20(5):622–8.
178. Cortright JJ, Lorrain DS, Beeler JA, Tang WJ, Vezina P. Previous exposure to delta9-tetrahydrocannibinol enhances locomotor responding to but not self-administration of amphetamine. J Pharmacol Exp Ther. 2011;337(3):724–33.
179. Vinklerova J, Novakova J, Sulcova A. Inhibition of methamphetamine self-administration in rats by cannabinoid receptor antagonist AM 251. J Psychopharmacol. 2002;16(2):139–43.
180. Schindler CW, Panlilio LV, Gilman JP, Justinova Z, Vemuri VK, Makriyannis A, et al. Effects of cannabinoid receptor antagonists on maintenance and reinstatement of methamphetamine self-administration in rhesus monkeys. Eur J Pharmacol. 2010;633(1–3):44–9.
181. Yu LL, Wang XY, Zhao M, Liu Y, Li YQ, Li FQ, et al. Effects of cannabinoid CB1 receptor antagonist rimonabant in consolidation and reconsolidation of methamphetamine reward memory in mice. Psychopharmacology. 2009;204(2):203–11.
182. Yu LL, Zhou SJ, Wang XY, Liu JF, Xue YX, Jiang W, et al. Effects of cannabinoid CB(1) receptor antagonist rimonabant on acquisition and reinstatement of psychostimulant reward memory in mice. Behav Brain Res. 2011;217(1):111–6.
183. Hiranita T, Nawata Y, Sakimura K, Yamamoto T. Methamphetamine-seeking behavior is due to inhibition of nicotinic cholinergic transmission by activation of cannabinoid CB1 receptors. Neuropharmacology. 2008;55(8):1300–6.
184. Rodriguez JS, Boctor SY, Flores LC, Phelix CF, Martinez JL, Jr. Local pretreatment with the cannabinoid CB1 receptor antagonist AM251 attenuates methamphetamine intra-accumbens self-administration. Neurosci Lett. 2011;489(3):187–91.
185. Anggadiredja K, Nakamichi M, Hiranita T, Tanaka H, Shoyama Y, Watanabe S, et al. Endocannabinoid system modulates relapse to methamphetamine seeking: possible mediation by the arachidonic acid cascade. Neuropsychopharmacology. 2004;29(8):1470–8.

186. Boctor SY, Martinez JL, Jr., Koek W, France CP. The cannabinoid CB1 receptor antagonist AM251 does not modify methamphetamine reinstatement of responding. Eur J Pharmacol. 2007;571(1):39–43.
187. Loewinger GC, Beckert MV, Tejeda HA, Cheer JF. Methamphetamine-induced dopamine terminal deficits in the nucleus accumbens are exacerbated by reward-associated cues and attenuated by CB1 receptor antagonism. Neuropharmacology. 2012;62(7):2192–201.
188. Wiskerke J, Stoop N, Schetters D, Schoffelmeer AN, Pattij T. Cannabinoid CB1 receptor activation mediates the opposing effects of amphetamine on impulsive action and impulsive choice. PloS one. 2011;6(10):e25856.
189. Parker LA, Burton P, Sorge RE, Yakiwchuk C, Mechoulam R. Effect of low doses of delta9-tetrahydrocannabinol and cannabidiol on the extinction of cocaine-induced and amphetamine-induced conditioned place preference learning in rats. Psychopharmacology. 2004;175(3):360–6.
190. Poncelet M, Barnouin MC, Breliere JC, Le Fur G, Soubrie P. Blockade of cannabinoid (CB1) receptors by 141716 selectively antagonizes drug-induced reinstatement of exploratory behaviour in gerbils. Psychopharmacology. 1999;144(2):144–50.
191. Tzavara ET, Davis RJ, Perry KW, Li X, Salhoff C, Bymaster FP, et al. The CB1 receptor antagonist SR141716 A selectively increases monoaminergic neurotransmission in the medial prefrontal cortex: implications for therapeutic actions. Br J Pharmacol. 2003;138(4):544–53.
192. Morra JT, Glick SD, Cheer JF. Neural encoding of psychomotor activation in the nucleus accumbens core, but not the shell, requires cannabinoid receptor signaling. J Neurosci. 2010;30(14):5102–7.
193. Morra JT, Glick SD, Cheer JF. Cannabinoid receptors mediate methamphetamine induction of high frequency gamma oscillations in the nucleus accumbens. Neuropharmacology. 2012;63(4):565–74.
194. Ferrer B, Gorriti MA, Palomino A, Gornemann I, de Diego Y, Bermudez-Silva FJ, et al. Cannabinoid CB1 receptor antagonism markedly increases dopamine receptor-mediated stereotypies. Eur J Pharmacol. 2007;559(2–3):180–3.
195. Marcellino D, Carriba P, Filip M, Borgkvist A, Frankowska M, Bellido I, et al. Antagonistic cannabinoid CB1/dopamine D2 receptor interactions in striatal CB1/D2 heteromers. A combined neurochemical and behavioral analysis. Neuropharmacology. 2008;54(5):815–23.
196. Houchi H, Babovic D, Pierrefiche O, Ledent C, Daoust M, Naassila M. CB1 receptor knockout mice display reduced ethanol-induced conditioned place preference and increased striatal dopamine D2 receptors. Neuropsychopharmacology. 2005;30(2):339–49.
197. Miller DK, Rodvelt KR, Constales C, Putnam WC. Analogs of SR-141716 A (Rimonabant) alter d-amphetamine-evoked [3H] dopamine overflow from preloaded striatal slices and amphetamine-induced hyperactivity. Life Sci. 2007;81(1):63–71.
198. Li X, Hoffman AF, Peng XQ, Lupica CR, Gardner EL, Xi ZX. Attenuation of basal and cocaine-enhanced locomotion and nucleus accumbens dopamine in cannabinoid CB1-receptor-knockout mice. Psychopharmacology. 2009;204(1):1–11.
199. Gorriti MA, Rodriguez de Fonseca F, Navarro M, Palomo T. Chronic (-)-delta9-tetrahydrocannabinol treatment induces sensitization to the psychomotor effects of amphetamine in rats. Eur J Pharmacol. 1999;365(2–3):133–42.
200. Landa L, Sulcova A, Slais K. Involvement of cannabinoid CB1 and CB2 receptor activity in the development of behavioural sensitization to methamphetamine effects in mice. Neuro Endocrinol Lett. 2006;27(1–2):63–9.
201. Corbille AG, Valjent E, Marsicano G, Ledent C, Lutz B, Herve D, et al. Role of cannabinoid type 1 receptors in locomotor activity and striatal signaling in response to psychostimulants. J Neurosci. 2007;27(26):6937–47.
202. Thiemann G, Di Marzo V, Molleman A, Hasenohrl RU. The CB(1) cannabinoid receptor antagonist AM251 attenuates amphetamine-induced behavioural sensitization while causing monoamine changes in nucleus accumbens and hippocampus. Pharmacol Biochem Behav. 2008;89(3):384–91.

203. Burchett SA, Hicks TP. The mysterious trace amines: protean neuromodulators of synaptic transmission in mammalian brain. Prog Neurobiol. 2006;79(5–6):223–46.
204. Xie Z, Miller GM. A receptor mechanism for methamphetamine action in dopamine transporter regulation in brain. J Pharmacol Exp Ther. 2009;330(1):316–25.
205. Tanda G, Pontieri FE, Di Chiara G. Cannabinoid and heroin activation of mesolimbic dopamine transmission by a common mu1 opioid receptor mechanism. Science. 1997;276(5321):2048–50.
206. Beltramo M, de Fonseca FR, Navarro M, Calignano A, Gorriti MA, Grammatikopoulos G, et al. Reversal of dopamine D(2) receptor responses by an anandamide transport inhibitor. J Neurosci. 2000;20(9):3401–7.
207. Gerdeman GL F-RJ. The endocannabinoid system in the physiology and pathophysiology of the basal ganglia. In: A K, editor. Cannabinoids and the brain. New York: Springer-Verlag; 2008. pp. 423–83.
208. Solinas M, Goldberg SR, Piomelli D. The endocannabinoid system in brain reward processes. Br J Pharmacol. 2008;154(2):369–83.
209. Sotnikova TD, Zorina OI, Ghisi V, Caron MG, Gainetdinov RR. Trace amine associated receptor 1 and movement control. Parkinsonism Relat Disord. 2008;14(Suppl 2):99–102.
210. Bradaia A, Trube G, Stalder H, Norcross RD, Ozmen L, Wettstein JG, et al. The selective antagonist EPPTB reveals TAAR1-mediated regulatory mechanisms in dopaminergic neurons of the mesolimbic system. Proc Natl Acad Sci U S A. 2009;106(47):20081–6.
211. Hernandez M, Berrendero F, Suarez I, Garcia-Gil L, Cebeira M, Mackie K, et al. Cannabinoid CB(1) receptors colocalize with tyrosine hydroxylase in cultured fetal mesencephalic neurons and their activation increases the levels of this enzyme. Brain Res. 2000;857(1–2):56–65.
212. Wenger T, Moldrich G, Furst S. Neuromorphological background of cannabis addiction. Brain Res Bull. 2003;61(2):125–8.
213. Lau T, Schloss P. The cannabinoid CB1 receptor is expressed on serotonergic and dopaminergic neurons. Eur J Pharmacol. 2008;578(2–3):137–41.
214. Laviolette SR, Grace AA. The roles of cannabinoid and dopamine receptor systems in neural emotional learning circuits: implications for schizophrenia and addiction. Cell Mol Life Sci: CMLS. 2006;63(14):1597–613.
215. Brown JA, Horvath S, Garbett K, Schmidt MJ, Everheart M, Gellert L, et al. The role of cannabinoid 1 receptor expressing interneurons in behavior. Neurobiol Dis. 2014;63:210–21.
216. Bortolato M, Frau R, Bini V, Luesu W, Loriga R, Collu M, et al. Methamphetamine neurotoxicity increases brain expression and alters behavioral functions of CB(1) cannabinoid receptors. J Psychiatr Res. 2010;44(14):944–55.
217. Piazza PV, Deminiere JM, Le Moal M, Simon H. Factors that predict individual vulnerability to amphetamine self-administration. Science. 1989;245(4925):1511–3.
218. Kelly TH, Robbins G, Martin CA, Fillmore MT, Lane SD, Harrington NG, et al. Individual differences in drug abuse vulnerability: d-amphetamine and sensation-seeking status. Psychopharmacology. 2006;189(1):17–25.
219. Giuffrida A, Parsons LH, Kerr TM, Rodriguez de Fonseca F, Navarro M, Piomelli D. Dopamine activation of endogenous cannabinoid signaling in dorsal striatum. Nat Neurosci. 1999;2(4):358–63.
220. Tzavara ET, Li DL, Moutsimilli L, Bisogno T, Di Marzo V, Phebus LA, et al. Endocannabinoids activate transient receptor potential vanilloid 1 receptors to reduce hyperdopaminergia-related hyperactivity: therapeutic implications. Biol Psychiatry. 2006;59(6):508–15.
221. Gardner EL. Endocannabinoid signaling system and brain reward: emphasis on dopamine. Pharmacol Biochem Behav. 2005;81(2):263–84.
222. Kleijn J, Wiskerke J, Cremers TI, Schoffelmeer AN, Westerink BH, Pattij T. Effects of amphetamine on dopamine release in the rat nucleus accumbens shell region depend on cannabinoid CB1 receptor activation. Neurochem Int. 2012;60(8):791–8.

223. Melis M, Pistis M, Perra S, Muntoni AL, Pillolla G, Gessa GL. Endocannabinoids mediate presynaptic inhibition of glutamatergic transmission in rat ventral tegmental area dopamine neurons through activation of CB1 receptors. J Neurosci. 2004;24(1):53–62.
224. Kreitzer AC, Malenka RC. Dopamine modulation of state-dependent endocannabinoid release and long-term depression in the striatum. J Neurosci. 2005;25(45):10537–45.
225. Yin HH, Lovinger DM. Frequency-specific and D2 receptor-mediated inhibition of glutamate release by retrograde endocannabinoid signaling. Proc Natl Acad Sci U S A. 2006;103(21):8251–6.
226. Shen W, Flajolet M, Greengard P, Surmeier DJ. Dichotomous dopaminergic control of striatal synaptic plasticity. Science. 2008;321(5890):848–51.
227. Chiu CQ, Puente N, Grandes P, Castillo PE. Dopaminergic modulation of endocannabinoid-mediated plasticity at GABAergic synapses in the prefrontal cortex. J Neurosci. 2010;30(21):7236–48.
228. Gubellini P, Picconi B, Bari M, Battista N, Calabresi P, Centonze D, et al. Experimental parkinsonism alters endocannabinoid degradation: implications for striatal glutamatergic transmission. J Neurosci. 2002;22(16):6900–7.
229. Lastres-Becker I, Cebeira M, de Ceballos ML, Zeng BY, Jenner P, Ramos JA, et al. Increased cannabinoid CB1 receptor binding and activation of GTP-binding proteins in the basal ganglia of patients with Parkinson's syndrome and of MPTP-treated marmosets. Eur J Neurosci. 2001;14(11):1827–32.
230. Di Marzo V Hill MP Bisogno T Crossman AR Brotchie JM. Enhanced levels of endogenous cannabinoids in the globus pallidus are associated with a reduction in movement in an animal model of Parkinson's disease. FASEB J. 2000;14(10):1432–8.
231. Kerr JN, Wickens JR. Dopamine D-1/D-5 receptor activation is required for long-term potentiation in the rat neostriatum in vitro. J Neurophysiol. 2001;85(1):117–24.
232 Calabresi P, Saiardi A, Pisani A, Baik JH, Centonze D, Mercuri NB, et al. Abnormal synaptic plasticity in the striatum of mice lacking dopamine D2 receptors. J Neurosci. 1997;17(12):4536–44.
233. Yamamoto Y, Nakanishi H, Takai N, Shimazoe T, Watanabe S, Kita H. Expression of N-methyl-D-aspartate receptor-dependent long-term potentiation in the neostriatal neurons in an in vitro slice after ethanol withdrawal of the rat. Neuroscience. 1999;91(1):59–68.
234. Kalivas PW, Sorg BA, Hooks MS. The pharmacology and neural circuitry of sensitization to psychostimulants. Behav Pharmacol. 1993;4(4):315–34.
235. Canales JJ, Capper-Loup C, Hu D, Choe ES, Upadhyay U, Graybiel AM. Shifts in striatal responsivity evoked by chronic stimulation of dopamine and glutamate systems. Brain. 2002;125(Pt 10):2353–63.
236. Capper-Loup C, Canales JJ, Kadaba N, Graybiel AM. Concurrent activation of dopamine D1 and D2 receptors is required to evoke neural and behavioral phenotypes of cocaine sensitization. J Neurosci. 2002;22(14):6218–27.
237. Szabo B, Muller T, Koch H. Effects of cannabinoids on dopamine release in the corpus striatum and the nucleus accumbens in vitro. J Neurochem. 1999;73(3):1084–9.
238. Szabo B, Siemes S, Wallmichrath I. Inhibition of GABAergic neurotransmission in the ventral tegmental area by cannabinoids. Eur J Neurosci. 2002;15(12):2057–61.
239. Robbe D, Alonso G, Duchamp F, Bockaert J, Manzoni OJ. Localization and mechanisms of action of cannabinoid receptors at the glutamatergic synapses of the mouse nucleus accumbens. J Neurosci. 2001;21(1):109–16.
240. Pistis M, Muntoni AL, Pillolla G, Gessa GL. Cannabinoids inhibit excitatory inputs to neurons in the shell of the nucleus accumbens: an in vivo electrophysiological study. Eur J Neurosci. 2002;15(11):1795–802.
241. Lupica CR, Riegel AC. Endocannabinoid release from midbrain dopamine neurons: a potential substrate for cannabinoid receptor antagonist treatment of addiction. Neuropharmacology. 2005;48(8):1105–16.
242. Wolf ME. The role of excitatory amino acids in behavioral sensitization to psychomotor stimulants. Prog Neurobiol. 1998;54(6):679–720.

243. Wise RA, Bozarth MA. A psychomotor stimulant theory of addiction. Psychol Rev. 1987;94(4):469–92.
244. Kalivas PW, Stewart J. Dopamine transmission in the initiation and expression of drug- and stress-induced sensitization of motor activity. Brain Res Brain Res Rev. 1991;16(3):223–44.
245. White FJ, Kalivas PW. Neuroadaptations involved in amphetamine and cocaine addiction. Drug Alcohol Depend. 1998;51(1–2):141–53.
246. Kalivas PW, Weber B. Amphetamine injection into the ventral mesencephalon sensitizes rats to peripheral amphetamine and cocaine. J Pharmacol Exp Ther. 1988;245(3):1095–102.
247. Vezina P, Stewart J. Amphetamine administered to the ventral tegmental area but not to the nucleus accumbens sensitizes rats to systemic morphine: lack of conditioned effects. Brain Res. 1990;516(1):99–106.
248. Jones S, Kornblum JL, Kauer JA. Amphetamine blocks long-term synaptic depression in the ventral tegmental area. J Neurosci. 2000;20(15):5575–80.
249. Tong ZY, Overton PG, Clark D. Chronic administration of (+)-amphetamine alters the reactivity of midbrain dopaminergic neurons to prefrontal cortex stimulation in the rat. Brain Res. 1995;674(1):63–74.
250. White FJ, Hu XT, Zhang XF, Wolf ME. Repeated administration of cocaine or amphetamine alters neuronal responses to glutamate in the mesoaccumbens dopamine system. J Pharmacol Exp Ther. 1995;273(1):445–54.
251. Fitzgerald LW, Ortiz J, Hamedani AG, Nestler EJ. Drugs of abuse and stress increase the expression of GluR1 and NMDAR1 glutamate receptor subunits in the rat ventral tegmental area: common adaptations among cross-sensitizing agents. J Neurosci. 1996;16(1):274–82.
252. Zhang XF, Hu XT, White FJ, Wolf ME. Increased responsiveness of ventral tegmental area dopamine neurons to glutamate after repeated administration of cocaine or amphetamine is transient and selectively involves AMPA receptors. J Pharmacol Exp Ther. 1997;281(2):699–706.
253. Cadogan AK, Alexander SP, Boyd EA, Kendall DA. Influence of cannabinoids on electrically evoked dopamine release and cyclic AMP generation in the rat striatum. J Neurochem. 1997;69(3):1131–7.
254. Glass M, Felder CC. Concurrent stimulation of cannabinoid CB1 and dopamine D2 receptors augments cAMP accumulation in striatal neurons: evidence for a Gs linkage to the CB1 receptor. J Neurosci. 1997;17(14):5327–33.
255. Gerdeman G, Lovinger DM. CB1 cannabinoid receptor inhibits synaptic release of glutamate in rat dorsolateral striatum. J Neurophysiol. 2001;85(1):468–71.
256. Herkenham M, Lynn AB, Johnson MR, Melvin LS, de Costa BR, Rice KC. Characterization and localization of cannabinoid receptors in rat brain: a quantitative in vitro autoradiographic study. J Neurosci. 1991;11(2):563–83.
257. Tsou K, Brown S, Sanudo-Pena MC, Mackie K, Walker JM. Immunohistochemical distribution of cannabinoid CB1 receptors in the rat central nervous system. Neuroscience. 1998;83(2):393–411.
258. Hermann H, Marsicano G, Lutz B. Coexpression of the cannabinoid receptor type 1 with dopamine and serotonin receptors in distinct neuronal subpopulations of the adult mouse forebrain. Neuroscience. 2002;109(3):451–60.
259. Julian MD, Martin AB, Cuellar B, Rodriguez De Fonseca F, Navarro M, Moratalla R, et al. Neuroanatomical relationship between type 1 cannabinoid receptors and dopaminergic systems in the rat basal ganglia. Neuroscience. 2003;119(1):309–18.
260. Martin AB, Fernandez-Espejo E, Ferrer B, Gorriti MA, Bilbao A, Navarro M, et al. Expression and function of CB1 receptor in the rat striatum: localization and effects on D1 and D2 dopamine receptor-mediated motor behaviors. Neuropsychopharmacology. 2008;33(7):1667–79.
261. Gonzalez B, Paz F, Floran L, Aceves J, Erlij D, Floran B. Cannabinoid agonists stimulate [3H]GABA release in the globus pallidus of the rat when G(i) protein-receptor coupling is restricted: role of dopamine D2 receptors. J Pharmacol Exp Ther. 2009;328(3):822–8.

262. Landa L, Jurajda M, Sulcova A. Altered dopamine D1 and D2 receptor mRNA expression in mesencephalon from mice exposed to repeated treatments with methamphetamine and cannabinoid CB1 agonist methanandamide. Neuro Endocrinol Lett. 2012;33(4):446–52.
263. Maneuf YP, Crossman AR, Brotchie JM. The cannabinoid receptor agonist WIN 55,212–2 reduces D2, but not D1, dopamine receptor-mediated alleviation of akinesia in the reserpine-treated rat model of Parkinson's disease. Exp Neurol. 1997;148(1):265–70.
264. Rodriguez de Fonseca F Del Arco I Martin-Calderon JL Gorriti MA Navarro M. Role of the endogenous cannabinoid system in the regulation of motor activity. Neurobiol Dis. 1998;5(6 Pt B):483–501.
265. Andersson M, Usiello A, Borgkvist A, Pozzi L, Dominguez C, Fienberg AA, et al. Cannabinoid action depends on phosphorylation of dopamine- and cAMP-regulated phosphoprotein of 32 kDa at the protein kinase A site in striatal projection neurons. J Neurosci. 2005;25(37):8432–8.
266. Lane DA, Chan J, Fitzgerald ML, Kearn CS, Mackie K, Pickel VM. Quinpirole elicits differential in vivo changes in the pre- and postsynaptic distributions of dopamine D(2) receptors in mouse striatum: relation to cannabinoid-1 (CB(1)) receptor targeting. Psychopharmacology. 2012;221(1):101–13.
267. Calabresi P, Maj R, Pisani A, Mercuri NB, Bernardi G. Long-term synaptic depression in the striatum: physiological and pharmacological characterization. J Neurosci. 1992;12(11):4224–33.
268. Choi S, Lovinger DM. Decreased probability of neurotransmitter release underlies striatal long-term depression and postnatal development of corticostriatal synapses. Proc Natl Acad Sci U S A. 1997;94(6):2665–70.
269. Centonze D, Gubellini P, Picconi B, Calabresi P, Giacomini P, Bernardi G. Unilateral dopamine denervation blocks corticostriatal LTP. J Neurophysiol. 1999;82(6):3575–9.
270. Kung VW, Hassam R, Morton AJ, Jones S. Dopamine-dependent long term potentiation in the dorsal striatum is reduced in the R6/2 mouse model of Huntington's disease. Neuroscience. 2007;146(4):1571–80.
271. Stern EA, Jaeger D, Wilson CJ. Membrane potential synchrony of simultaneously recorded striatal spiny neurons in vivo. Nature. 1998;394(6692):475–8
272. Chiang YC, Chen JC. The role of the cannabinoid type 1 receptor and down-stream cAMP/DARPP-32 signal in the nucleus accumbens of methamphetamine-sensitized rats. J Neurochem. 2007;103(6):2505–17.
273. Calabresi P, Gubellini P, Centonze D, Picconi B, Bernardi G, Chergui K, et al. Dopamine and cAMP-regulated phosphoprotein 32 kDa controls both striatal long-term depression and long-term potentiation, opposing forms of synaptic plasticity. J Neurosci. 2000;20(22):8443–51.
274. Kearn CS, Blake-Palmer K, Daniel E, Mackie K, Glass M. Concurrent stimulation of cannabinoid CB1 and dopamine D2 receptors enhances heterodimer formation: a mechanism for receptor cross-talk? Mol Pharmacol. 2005;67(5):1697–704.
275. Huang YC, Wang SJ, Chiou LC, Gean PW. Mediation of amphetamine-induced long-term depression of synaptic transmission by CB1 cannabinoid receptors in the rat amygdala. J Neurosci. 2003;23(32):10311–20.
276. Chavez AE, Chiu CQ, Castillo PE. TRPV1 activation by endogenous anandamide triggers postsynaptic long-term depression in dentate gyrus. Nat Neurosci. 2010;13(12):1511–8.
277. Mezey E, Toth ZE, Cortright DN, Arzubi MK, Krause JE, Elde R, et al. Distribution of mRNA for vanilloid receptor subtype 1 (VR1), and VR1-like immunoreactivity, in the central nervous system of the rat and human. Proc Natl Acad Sci U S A. 2000;97(7):3655–60.
278. Bisogno T, Hanus L, De Petrocellis L, Tchilibon S, Ponde DE, Brandi I, et al. Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. Br J Pharmacol. 2001;134(4):845–52.
279. Costa B, Giagnoni G, Franke C, Trovato AE, Colleoni M. Vanilloid TRPV1 receptor mediates the antihyperalgesic effect of the nonpsychoactive cannabinoid, cannabidiol, in a rat model of acute inflammation. Br J Pharmacol. 2004;143(2):247–50.

280. De Petrocellis L, Ligresti A, Moriello AS, Allara M, Bisogno T, Petrosino S, et al. Effects of cannabinoids and cannabinoid-enriched Cannabis extracts on TRP channels and endocannabinoid metabolic enzymes. Br J Pharmacol. 2011;163(7):1479–94.
281. Moreira FA, Guimaraes FS. Cannabidiol inhibits the hyperlocomotion induced by psychotomimetic drugs in mice. Eur J Pharmacol. 2005;512(2–3):199–205.
282. Starowicz K, Nigam S, Di Marzo V. Biochemistry and pharmacology of endovanilloids. Pharmacol Ther. 2007;114(1):13–33.
283. Hu SS, Bradshaw HB, Benton VM, Chen JS, Huang SM, Minassi A, et al. The biosynthesis of N-arachidonoyl dopamine (NADA), a putative endocannabinoid and endovanilloid, via conjugation of arachidonic acid with dopamine. Prostaglandins Leukot Essent Fatty Acids. 2009;81(4):291–301.
284. Bobrov MY, Lizhin AA, Andrianova EL, Gretskaya NM, Frumkina LE, Khaspekov LG, et al. Antioxidant and neuroprotective properties of N-arachidonoyldopamine. Neurosci Lett. 2008;431(1):6–11.
285. Oz M, Jaligam V, Galadari S, Petroianu G, Shuba YM, Shippenberg TS. The endogenous cannabinoid, anandamide, inhibits dopamine transporter function by a receptor-independent mechanism. J Neurochem. 2010;112(6):1454–64.
286. Onaivi ES, Green MR, Martin BR. Pharmacological characterization of cannabinoids in the elevated plus maze. J Pharmacol Exp Ther. 1990;253(3):1002–9.
287. Ortega-Alvaro A, Aracil-Fernandez A, Garcia-Gutierrez MS, Navarrete F, Manzanares J. Deletion of CB2 cannabinoid receptor induces schizophrenia-related behaviors in mice. Neuropsychopharmacology. 2011;36(7):1489–504.
288. Nossoll M, Teuchert-Noodt G, Dawirs RR. A single dose of methamphetamine in neonatal gerbils affects adult prefrontal gamma-aminobutyric acid innervation. Eur J Pharmacol. 1997;340(2–3):R3–5.
289. Gonzalez R, Rippeth JD, Carey CL, Heaton RK, Moore DJ, Schweinsburg BC, et al. Neurocognitive performance of methamphetamine users discordant for history of marijuana exposure. Drug Alcohol Depend. 2004;76(2):181–90.
290. Jin KL, Mao XO, Goldsmith PC, Greenberg DA. CB1 cannabinoid receptor induction in experimental stroke. Ann Neurol. 2000;48(2):257–61.
291. Fernandez-Lopez D, Martinez-Orgado J, Nunez E, Romero J, Lorenzo P, Moro MA, et al. Characterization of the neuroprotective effect of the cannabinoid agonist WIN-55212 in an in vitro model of hypoxic-ischemic brain damage in newborn rats. Pediatr Res. 2006;60(2):169–73.
292. Nagayama T, Sinor AD, Simon RP, Chen J, Graham SH, Jin K, et al. Cannabinoids and neuroprotection in global and focal cerebral ischemia and in neuronal cultures. J Neurosci. 1999;19(8):2987–95.
293. Marsicano G, Goodenough S, Monory K, Hermann H, Eder M, Cannich A, et al. CB1 cannabinoid receptors and on-demand defense against excitotoxicity. Science. 2003;302(5642):84–8.
294. Marchalant Y, Rosi S, Wenk GL. Anti-inflammatory property of the cannabinoid agonist WIN-55212–2 in a rodent model of chronic brain inflammation. Neuroscience. 2007;144(4):1516–22.
295. Solbrig MV, Hermanowicz N. Cannabinoid rescue of striatal progenitor cells in chronic Borna disease viral encephalitis in rats. J Neurovirol. 2008;14(3):252–60.
296. van der Stelt M, Di Marzo V. Cannabinoid receptors and their role in neuroprotection. Neuromolecular Med. 2005;7(1–2):37–50.
297. Romero J, Berrendero F, Perez-Rosado A, Manzanares J, Rojo A, Fernandez-Ruiz JJ, et al. Unilateral 6-hydroxydopamine lesions of nigrostriatal dopaminergic neurons increased CB1 receptor mRNA levels in the caudate-putamen. Life Sci. 2000;66(6):485–94.
298. Shen M, Piser TM, Seybold VS, Thayer SA. Cannabinoid receptor agonists inhibit glutamatergic synaptic transmission in rat hippocampal cultures. J Neurosci. 16(14):4322–34.
299. Shen M, Thayer SA. Cannabinoid receptor agonists protect cultured rat hippocampal neurons from excitotoxicity. Mol Pharmacol. 1998;54(3):459–62.

300. Nadler V, Mechoulam R, Sokolovsky M. Blockade of 45Ca2+ influx through the N-methyl-D-aspartate receptor ion channel by the non-psychoactive cannabinoid HU-211. Brain Res. 1993;622(1–2):79–85.
301. Hampson AJ, Grimaldi M, Axelrod J, Wink D. Cannabidiol and (-)Delta9-tetrahydrocannabinol are neuroprotective antioxidants. Proc Natl Acad Sci U S A. 1998;95(14):8268–73.
302. Borges RS, Batista J, Jr., Viana RB, Baetas AC, Orestes E, Andrade MA, et al. Understanding the molecular aspects of tetrahydrocannabinol and cannabidiol as antioxidants. Molecules. 2013;18(10):12663–74.
303. Lavie G, Teichner A, Shohami E, Ovadia H, Leker RR. Long term cerebroprotective effects of dexanabinol in a model of focal cerebral ischemia. Brain Res. 2001;901(1–2):195–201.
304. Leker RR, Shohami E, Abramsky O, Ovadia H. Dexanabinol; a novel neuroprotective drug in experimental focal cerebral ischemia. J Neurol Sci. 1999;162(2):114–9.
305. Louw DF, Yang FW, Sutherland GR. The effect of delta-9-tetrahydrocannabinol on forebrain ischemia in rat. Brain Res. 2000;857(1–2):183–7.
306. Panikashvili D, Simeonidou C, Ben-Shabat S, Hanus L, Breuer A, Mechoulam R, et al. An endogenous cannabinoid (2-AG) is neuroprotective after brain injury. Nature. 2001;413(6855):527–31.
307. Sinor AD, Irvin SM, Greenberg DA. Endocannabinoids protect cerebral cortical neurons from in vitro ischemia in rats. Neurosci Lett. 2000;278(3):157–60.
308. van der Stelt M, Veldhuis WB, van Haaften GW, Fezza F, Bisogno T, Bar PR, et al. Exogenous anandamide protects rat brain against acute neuronal injury in vivo. J Neurosci. 2001;21(22):8765–71.
309. Knoller N, Levi L, Shoshan I, Reichenthal E, Razon N, Rappaport ZH, et al. Dexanabinol (HU-211) in the treatment of severe closed head injury: a randomized, placebo-controlled, phase II clinical trial. Crit Care Med. 2002;30(3):548–54.
310. Bortolato M, Piomelli D. The endocannabinoid system and anxiety responses. In: Blanchard RJ BD, Griebel G, Nutt D, editors. Hand book of Anxiety and Fear. Amsterdam: Elsevier; 2008. pp. 303–25.