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Invited review

Modulation and functions of dopamine receptor heteromers in drugs of abuse-induced adaptations

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HIGHLIGHTS

- Many DAR heteromers have been identified but their biological significance is only emerging.
- Targeting DAR heteromers has a strong therapeutic potential the field of addiction.
- The selective inhibition of receptor heteromers is a major limitation to uncover their roles in *vivo*.

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ABSTRACT

Drug addiction is a chronic and relapsing disorder that leads to compulsive drug intake despite deleterious consequences. By increasing dopamine (DA) in the mesolimbic system, drugs of abuse hijack the brain reward circuitry, which is critical for the development of enduring behavioral alterations. DA mainly acts onto DA D1 (D1R) and D2 (D2R) receptor subtypes, which are positively and negatively coupled to adenylyl cyclase, respectively. Extensive research has aimed at targeting these receptors for the treatment of addiction, however this often results in unwanted side-effects due to the implication of DA receptors in numerous physiological functions. A growing body of evidence indicates that the physical interaction of DA receptors with other receptors can finely tune their function, making DA receptor heteromers promising targets for more specific treatment strategies. An increasing number of articles highlighted the ability of both D1R and D2R to form heteromers, however, most studies carried out to date stem from observations in heterologous systems and the biological significance of DA receptor heteromers *in vivo* is only emerging. We focused this review on studies that were able to provide insights into functions on D1R and D2R heteromers in drug-evoked adaptations and discuss the limitations of current approaches to study receptor heteromers *in vivo*.

This article is part of the Special Issue entitled 'Receptor heteromers and their allosteric receptor-receptor interactions'.

1. Introduction

Drug addiction is a chronic and relapsing disorder that results from protracted drug consumption by vulnerable individuals, leading to compulsive drug intake despite deleterious consequences. Drug-evoked neuronal activity changes within the so-called brain reward circuit are fundamental for the instatement of the enduring behavioral alterations that are characteristic of addiction (Lüscher and Malenka, 2011). Such

Abbreviations: A2AR, adenosine A2A receptor; BRET, bioluminescence resonance energy transfer; CaMKII, Calcium Calmodulin-dependent protein kinase II; CTD, C-terminal domain; DA, dopamine; D1R, dopamine receptor type 1; D2R, dopamine receptor type 2; ERK1/2, extracellular signal-regulated kinase 1/2; FRET, fluorescence resonance energy transfer; GPCR, G protein-coupled receptor; IL, intracellular loop; MSN, medium sized-spiny neurons; NAcc, nucleus accumbens; NMDAR, N-methyl-D-aspartate glutamate receptor; PET, positron emission tomography; PKC, protein kinase C; PLA, proximity ligation assay; PSD, post synaptic density; TM, transmembrane domain

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Table 1
Modulation and functions of endogenous dopamine receptor heteromers in response to drugs of abuse *in vivo*.

Psychostimulant-Animal model	Dopamine receptor heteromer modulation	Impact on drug-evoked responses	References
Rat; acute cocaine (30mg/kg i.p)	D2R/GluN2B heteromers 30 min post-cocaine in the NAcc and dStr.	D2R/GluN2B disruption with Tat-D2R-IL3 (intravenous): ● Inhibition of cocaine-induced decrease in phospho-Ser^{1303} GluN2B. ● Acute hyperlocomotion & stereotypies	Liu et al. 2006
Mouse; cocaine (15mg/kg i.p) & striatal cultures	D1R/GluN1 10 min after a co-stimulation of D1R and NMDAR	D1R/GluN1 disruption with Tat-GluN1-C1 (infusion into the NAcc): ● Blockade of striatal LTP. ● Inhibition of cocaine-induced ERK1/2 activation. ● Preservation of basal locomotion & acute hyperlocomotor response to cocaine. ● Alteration of cocaine-mediated locomotor sensitization induced by 2 injections.	Cahill et al., 2014b
Rat; cocaine self-administration FR5 (0.5mg/kg per infusion i.v)	D2R/A2AR heteromers 2 hours after the last self-administration session in the NAcc shell.	D2R/A2AR disruption with SynthTM5 (infusion in the NAcc): ● Prevents the decrease in self-administration induced by i.p. administration of CGS 21680.	Borroto-Escuela et al., 2017a; 2018a
Rat; amphetamine sensitization (1.5mg/kg i.p)		Subchronic D2R/D1R disruption with Tat-D1 (i.c.v. injection): ● Enhances locomotion ● Prevents the decrease in sensitization induced by s.c. administration of SKF83959.	Shen et al., 2015b
Rat; cocaine locomotor sensitization (10mg/kg i.p); conditioned place preference (10 mg/kg i.p) cocaine self-administration (0.25 mg/infusion i.v)	Tat-D1 (i.c.v. injection) prevents the increase in D1R/D2R co-immunoprecipitation induced by SKFss83959	D2R/D1R disruption with Tat-D1 (i.c.v. injection): ● Enhances the acute locomotor effect of cocaine as well as sensitization. ● Induces conditioned place-preference ● Enhances conditioned-place preference induced by cocaine administration ● Enhances reinstatement of self-administration response after extinction by a single cocaine injection. ● Enhances delatFosB expression after repeated (7 days) injection. ● Prevents the conditioned place aversion induced by administration of SKF83959 ● Reverses the antagonistic effect of SKF83959 on cocaine conditioned place preference	Perreault et al., 2016; Hasbi et al., 2018

modulations of synaptic efficacy are translated into specific patterns of signaling pathway activation and gene expression driving a long-lasting remodeling of neural circuits, likely involved in the transition from casual to compulsive drug intake and addiction (Nestler, 2001, 2014).

Despite their distinct targets, all drugs of abuse hijack the natural reward system by increasing dopamine (DA) concentration in the mesolimbic system, especially in the striatum (Di Chiara and Imperato, 1988), resulting in alterations in glutamate transmission-dependent plasticity (Lüscher and Malenka, 2011). The striatum is considered a key target structure of drugs of abuse within the reward circuit because it is at the crossroad of converging glutamate signals arising from limbic, thalamic and cortical regions, which encode components of drug-associated stimuli and environment, along with DA transmission that mediates reward prediction error and incentive values.

This integration of DA and glutamate inputs is mainly accomplished by the Medium-sized Spiny GABAergic Neurons (MSN), which receive glutamate axon terminals and DA afferences converging on MSN dendritic spines (Moss and Bolam, 2008; Doig et al., 2010). MSN form primarily two segregated populations based on the expression of either DA D1 (D1R) or DA D2 (D2R) receptors, which are G protein-coupled receptors (GPCR) positively and negatively coupled to adenylyl cyclase though their respective coupling to $G_{s/olf}$ and $G_{i/o}$ subtypes (Felder et al., 1991; Corvol et al., 2001), although a fraction of MSN in the ventral striatum (i.e. nucleus accumbens; NAcc) express both receptors (Bertran-Gonzalez et al., 2008).

These two sub-populations of MSN also display distinct projections within the cortico-basal ganglia network with the D1R-MSN and D2R-MSN forming the direct pathway (dMSN) and the indirect pathway (iMSN), respectively. In the dorsal part of the striatum, dMSN and iMSN exert opposite functions regarding the control of motor behavior. Optogenetic stimulations of dorsal dMSN and iMSN has been shown to promote and inhibit locomotion, respectively (Kravitz et al., 2010).

Within the NAcc, this functional dichotomy also applies to reward-dependent learning since the activation of the direct pathway neurons promotes reward whereas the stimulation of indirect pathway neurons is associated with punishment (Hikida et al., 2010; Lobo et al., 2010; Kravitz et al., 2012).

The surge of DA induced by drugs of abuse thus triggers a stimulation of D1R that activates dMSN and promotes reiforcement, whereas the D2R-mediated inhibition iMSN opposes to aversion, explaining why a high rewarding value of a stimuli is set when both D1R and D2R are stimulated. Based on these observations, it has been proposed that the imbalance between the activity of dMSN and iMSN evoked by drugs of abuse may drive towards compulsive drug intake and addiction (Lobo and Nestler, 2011; Volkow and Morales, 2015).

We and others have started to identify the underlying cellular and molecular mechanisms (Girault et al., 2007; Cahill et al., 2014a; Pascoli et al., 2014a). We found that a single cocaine administration triggers a D1R-mediated facilitation of N-methyl-D-aspartate glutamate receptors (NMDAR) that activates in dMSN the extracellular signal-regulated kinase1/2 (ERK1/2), which controls epigenetic and genic responses that are mandatory for the development of long-term behavioral alterations (Pascoli et al., 2011a, 2014a,b).

Although the implication of DA and glutamate signaling crosstalk in drug-evoked neuronal adaptations is well acknowledged, targeting the cognate receptors to alleviate symptoms is associated with a loss of efficacy over time and the appearance of severe sides effects, likely due to the involvement of these receptors in fundamental physiological

functions (Wang et al., 2012; Cahill et al., 2014a). Instead, a selective targeting of the molecular mechanisms responsible for the modulation of excitatory transmission by DA appears as a promising strategy.

Beside local intracellular cascades downstream from DA receptors, a growing body of evidence supports that the physical interaction between receptors is a powerful mechanism by which receptors can mutually modify their functions through allosteric modulations. The formation of such receptor oligomers can engage two, or more, identical (homomers) or distinct (heteromers) receptors. These receptor complexes have been the subject of intense investigation because they can fine-tune downstream signaling and binding affinity of the component receptors in a spatio-temporal manner, which makes them attractive for the development of more selective pharmacological treatments for numerous neurological and psychiatric diseases (Missale et al., 2006, 2013; Borroto-Escuela et al., 2017a, 2017b). DA receptors have been shown – mostly in heterologous systems – to form many heteromers with other GPCR, ionotropic channels and transmembrane proteins, resulting in functional changes of partner receptors, modification of binding affinity for ligands and biased signaling. The diversity and biophysical properties of DA receptor heteromers have been exhaustively reviewed elsewhere (Wang et al., 2012; Ferré et al., 2016). Moreover, numerous studies showed the critical role of the physical interaction between DA receptors and NMDAR for their reciprocal modulation (Lee et al., 2002; Pei et al., 2004; Cepeda and Levine, 2006; Wang et al., 2012; Ladepeche et al., 2013), which makes them particularly relevant for drug addiction.

The current review focuses on reports that were able to provide proof of concept that endogenous DA receptor heteromers in the brain can be modulated in response to exposure to drugs of abuse and eventually participate to drug-evoked neuronal adaptations (Table 1). For each DA receptor heteromer, we start from its historical discovery in heterologous systems, the identification of the protein-protein interaction domains and associated changes in signaling, to finally discuss their modulation *in vivo* and the strategies used to establish their potential roles in drug-evoked adaptations.

2. D2R heteromers and addiction

Notably because alterations of D2R-mediated signaling have been associated with numerous pathologies, there has been extensive work to identify putative heteromers formed by the D2R. Most of them were characterized in heterologous systems by bioluminescence or fluorescence resonance transfer (BRET/FRET) analyses, co-immunoprecipitation, or indirectly through modulation of ligand binding affinity and signaling effectors. These studies led to the identification of numerous and diverse receptors that are able to form complexes with the D2R and alter downstream signaling through allosteric modulations, as extensively reviewed (see Fuxe et al., 2014; Borroto-Escuela and Fuxe, 2017). Herein, we focus on D2R heteromers for which a functional impact has been characterized *in vivo*.

2.1. D2R/A2AR heteromers

The purinergic system plays an antagonistic role onto DA transmission, an effect mainly achieved through the adenosine A2A receptor (A2AR), which expression is restricted to iMSN (Schiffman et al., 2007) where it is highly colocalized with the D2R. As suggested by proximity-ligation assay (PLA) on striatal tissue, a subset of A2AR and D2R are in close proximity, which supports the existence of A2AR/D2R heteromers *in vivo* (Trifilieff et al., 2011; Fernandez-Duenas et al., 2015; He et al., 2016; Borroto-Escuela et al., 2017a, 2018a).

Historically, the work on interactions between striatal adenosine and dopamine signaling began with the original observation that caffeine and theophyllamine, which antagonize adenosine receptors, were able to enhance the antiparkinson actions of levodopa and DAR agonists in a model of hemiparkinson rats (Fuxe and Ungerstedt, 1974). Later on, the first indirect evidence for the existence of D2R/A2AR heteromers came from the observation that the A2AR agonist CGS 21680 was able to decrease D2R affinity for the agonist apomorphine in native membranes prepared from the rat striatum, suggesting allosteric modulations within D2R/A2AR complexes (Ferré et al., 1991). Since this discovery, extensive work, mainly by Ferré's and Fuxe's groups, characterized the biophysical and pharmacological properties of D2R/A2AR heteromers, which have become a model study of allosteric modulation between GPCR (Ferré et al., 2018; Borroto-Escuela et al., 2018a). The extensive description of the biophysical properties of D2R/A2AR heteromers is out of the scope of the current article but remarkable recent reviews can be recommended (Ferré et al., 2016, 2018). A current model developed by Ferré and collaborators propose that A2AR/A2AR and D2R/D2R homodimers, coupled to their respective G protein – $G_{s/olf}$ and $G_{i/o}$, constitute an heterotetrameric structure forming a macromolecular complex with type 5 adenylate cyclase (AC5) (Navarro et al., 2018; Ferré et al., 2018). Electrostatic interactions between transmembrane domains (TM) 6 form the homodimer interface, while heteromeric interactions involve TM 4 and 5 of one receptor within each homodimer (see Navarro et al., 2018). D2R/A2AR heteromerization results in negative allosteric interactions by which A2AR ligands – agonists and antagonists - decrease the affinity and efficacy of D2R ligands (Azdad et al., 2009; Bonaventura et al., 2015) and, reciprocally, D2R agonists inhibit A2AR-dependent activation of AC5 (Navarro et al., 2018). In terms of signaling, this antagonistic interaction would result in a switch from cyclic AMP- to PLC- and arrestin-dependent pathways, whether stimulation of A2AR or D2R, respectively, is dominant (Borroto-Escuela et al., 2011; see Ferré et al., 2018 for review).

These unique properties of D2R/A2AR heteromers have opened new routes for pharmacological strategies for pathologies related to alterations in DA transmission. For instance, even though the direct dependence to D2R/A2AR heteromers has not been demonstrated, preclinical evidence support some efficacy of A2AR antagonists to alleviate symptoms in Parkinson's disease (Salamone et al., 2013; Podurgiel et al., 2016) or apathy – i.e. loss of motivation (Mott et al., 2009; Salamone et al., 2009; Pardo et al., 2012; Nunes et al., 2013; Randall et al., 2014; Lopez-Cruz et al., 2018). Recently, Volkow and colleagues showed that the psychostimulant caffeine, a potent A2AR antagonist, enhances D2R availability in healthy control subjects measure by Positron Emission Tomography (PET) (Volkow et al., 2015). It is unclear whether this effect results from upregulation of membrane expression of D2R or change in their binding affinity for the radioligand (^{11}C)-Raclopride, but Ferré and colleagues proposed that it could directly result from the "ability of caffeine to antagonize the effect of endogenous adenosine on the binding of exogenous D2R antagonist" (Ferré et al., 2018). This hypothesis remains to be tested but these observations highlight the potential interest of D2R/A2AR heteromerization in the modulation of D2R activity and binding affinity. Yet, a decrease in striatal D2R availability in subjects suffering from drug addiction is one of the most consistent findings in PET imaging (Koob and Volkow, 2016; Trifilieff et al., 2017). The causes for such decrease are still unclear and could be both a consequence of drug exposure and/or a vulnerability factor for drug abuse. Nevertheless, this neurobiological feature is likely to constitute a central mechanism for the development of addiction (Trifilieff and Martinez, 2014). Because the use of selective D2R ligands would impact crucial physiological functions and lead to severe unwanted side-effects, compounds that could act as allosteric modulators of D2R activity are a promising strategy in the field of addiction. In this context, D2R/A2AR heteromerization should be considered as a potential target.

Accordingly, preclinical data suggest that D2R/A2AR heteromerization could be involved in some aspects of addiction for psychostimulants. Extended cocaine self-administration resulted in an increased binding for (^{3}H)-ZM 241385 – an A2AR antagonist – in the NAcc of rats, which was reversed after extinction or withdrawal

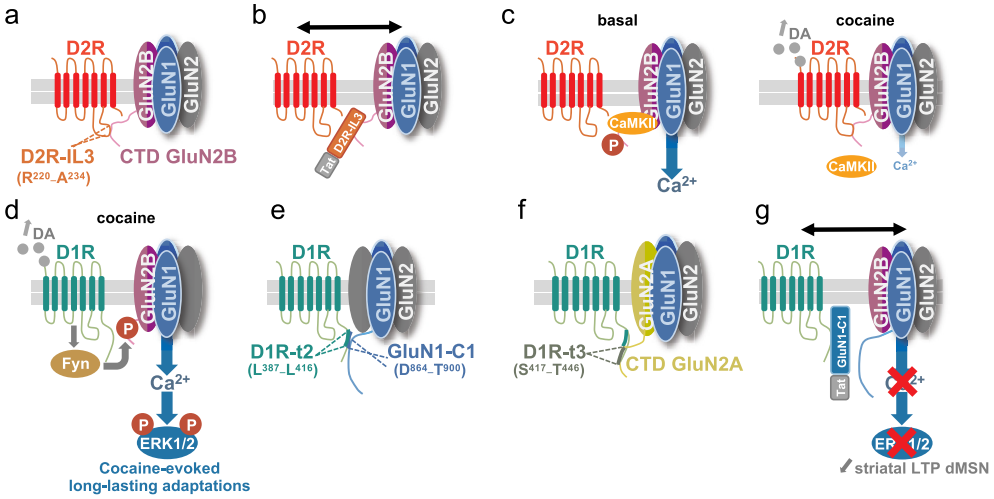

Fig. 1. Formation, regulation and functions of heteromers formed dopamine and NMDA receptors in response to drugs of abuse. (a) Diagram depicting the formation of D2R/GluN2B-NMDAR heteromers through the interaction of a fragment of the D2R-IL3 with the CTD of GluN2B. **(b)** Mode of action of the cell-permeable Tat-D2R-IL3 peptide, which disrupt D2R/GluN2B interaction. **(c)** A single cocaine administration favors D2R/GluN2B heteromerization in the striatum. Consequently, the binding of CaMKII to GluN2B is altered, which decreases GluN2B phosphorylation of Ser^{1303} and inhibits NMDAR functions in D2R-MSN (see Liu et al., 2006). **(d)** In D1R-MSN, stimulation of D1R triggers a D1R-dependent, and Fyn-mediated, phosphorylation of GluN2B on Tyr^{1472}, which triggers a downstream Ca^{2+}-dependent activation of ERK1/2 controlling cocaine-induced long-term adaptations (see Pascoli et al., 2011a, 2014a). Schematic representation of D1R/GluN1 **(e)** and D1R/Glu2A **(f)** heteromerization. **(g)** The disruption of D1R/GluN1 heteromers with the Tat-GluN1-C1 blocks the facilitation of Glu2NB-NMDAR by D1R and downstream ERK activation and striatal LTP in dMSN, while preserving the function of individual D1R and NMDAR (see Cahill et al., 2014b).

(Marcellino et al., 2007; Frankowska et al., 2013). Moreover, cocaine self-administration increases D2R/A2AR complexes in the shell of the NAcc (Borroto-Escuela et al., 2017a). The functional significance of this increased D2R/A2AR heteromerization was assessed with an interfering peptide corresponding to the TM5 of A2AR, which prevents D2R/A2AR interaction in heterologous system. Local administration of this peptide in the NAcc of rats the last 2 days of cocaine self-administration prevented the decrease in self-administration induced by injection of the A2AR agonist CGS 21680. Specificity of the TM5 interfering peptide was verified by showing that administration of a peptide corresponding to the TM2 of A2AR, which preserves D2R/A2AR interaction, had no effect (Borroto-Escuela et al., 2018b). Further work is necessary to characterize the impact of alterations of D2R/A2AR heteromers on psychostimulants self-administration. However, the fact that this allosteric interaction results in an inhibition of D2R-dependent transmission suggests that preventing the formation of D2R/A2AR heteromers could be an efficient strategy to modulate D2R activity, which is blunted in substance use disorders.

Of note, the D2R/A2AR interaction could also take place within higher-order oligomers. As an example, complexes with metabotropic glutamate type 5 receptors (mGluR5) have been detected by co-immunoprecipitation from striatal tissue (Cabello et al., 2009). Pharmacological experiments suggest that, within this receptor complex, A2AR and mGluR receptors could act synergistically to inhibit D2R (Beggiato et al., 2016). The D2R has also been shown to form higher-order heteromers with the sigma-1 receptor, which is able to directly bind cocaine (Navarro et al., 2013; Beggiato et al., 2017). These complexes have been detected in the striatum (Beggiato et al., 2017) but their functional implication in cocaine-induced adaptations remain to be demonstrated.

2.2. D2R/GluN2B heteromers

The integration of DA- and glutamate-dependent signaling within the reward circuitry plays functional roles in drugs of abuse-evoked long-lasting alterations (Lüscher and Malenka, 2011; Pascoli et al., 2014a; Bellone and Gardoni, 2015). In addition to mGluR, glutamate binds to ionotropic receptors of the α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPAR), kainate and NMDA subtypes, which mediate most of the excitatory neurotransmission in the brain and play key roles in synaptic plasticity (Traynelis et al., 2010).

NMDAR are voltage-gated calcium (Ca^{2+}) channels playing pivotal roles in modulating synaptic transmission. Alterations of their functions have been associated with numerous developmental, neurological and psychiatric disorders, including addiction (Lau and Zukin, 2007). NMDAR are heteromeric structures composed of two obligatory GluN1 subunits (formerly named NR1) and two regulatory GluN2 (GluN2A, GluN2B, GluN2C, GluN2D) and/or GluN3 subunits (GluN3A, GluN3B). Depending on the subunit composition, NMDAR fall into two main categories, the di-heteromeric (GluN1 with identical GluN2) or the tri-heteromeric ones, composed of GluN1 associated to a mixture of GluN2 and/or GluN3 subunits. Most differences between these subunits mainly reside in their intracellular C-terminal domains (CTD), which are subjected to post-translational modifications controlling NMDAR trafficking, protein interactions, Ca^{2+} dynamics and coupling to specific pathways (Paoletti et al., 2013). Among other post-translational modifications, Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) (Omkumar et al., 1996) and protein kinase C (PKC) (Liao et al., 2001) can phosphorylate the GluN2B CTD on Ser^{1303}, which enhances NMDA currents (Lieberman and Mody, 1994; Liao et al., 2001), notably by favoring NMDAR surface expression (Jin et al., 2015).

In an attempt to identify the molecular mechanisms underlying the integration of DA and NMDA-mediated signals in response to drugs of abuse, Liu and coworkers highlighted a direct physical interaction between D2R and GluN2B subunits in post synaptic density (PSD) fractions of the rat hippocampus, prefrontal cortex and striatum (Liu et al., 2006). They observed that a single cocaine injection triggers an increased D2R/GluN2B heteromerization in the NAcc and dorsal striatum, paralleled by a decrease of phospho-GluN2B-Ser^{1303}. This was strictly dependent on D2R signaling since the D2R antagonist Eticlopride blocked both cocaine-mediated inhibition of phospho-GluN2B-Ser^{1303} and D2R/GluN2B interaction, while a D2R agonist had opposite effects. The protein domains involved in D2R/GluN2B interaction were then characterized and the residues R^{220}-A^{234} within third intracellular loop of D2R (D2R-IL3) appeared as critical for the binding of D2R to the CTD of GluN2B (Fig. 1a). By using a penetrating peptide corresponding this R^{220}-A^{234} -D2R-IL3 fragment, which disrupts D2R/GluN2B heteromers (Fig. 1b), it was shown that the cocaine-induced stimulation of D2R facilitates the D2R/GluN2B interaction, leading to a decrease of NMDAR currents in iMSN. This inhibition of NMDAR relies on a competition mechanism whereby D2R/GluN2B heteromers induced by cocaine disrupt the binding of CaMKII to GluN2B and reduces CaMKII activity (Fig. 1c). At the behavioral level, disruption of D2R/GluN2B interaction inhibits the acute hyperlocomotion and stereotypies induced by a single high dose of cocaine (Liu et al., 2006). This pioneer study strongly supports the hypothesis that D2R/GluN2B heteromers

could mediate the inhibitory effects of psychostimulants on iMSNs. However, it raises several important questions that we are currently pursuing. With regard to the chronic nature of addiction-related disorders, it would be important to determine how D2R/GluN2B heteromers are modulated in response to repeated exposure cocaine and if disrupting D2R/GluN2B interaction could overcome cocaine-evoked long-lasting responses. Furthermore, the R^{220}-A^{234} -D2R-IL3 peptide used to alter D2R/GluN2B interaction comprises a part of the Arginine-rich domain of D2R that is critical for its binding to A2AR (Ciruela et al., 2004; see section 2.1). Using a shorter D2R-IL3 peptide that selectively alters D2R/GluN2B interaction would definitely precise the specific role of D2R/GluN2B in long-term effects of drugs of abuse. This is particularly relevant in light of recent evidence showing that D2R-mediated inhibition of NMDAR also involves D2R/A2AR interaction (Azdad et al., 2009).

2.3. D1R/D2R heteromers

Another DA receptor heteromer that has been extensively studied, mostly by the group of Susan R. George, is the one formed by the D1R and D2R. Co-expression of both receptors in the striatum has been reported mostly in the shell of the NAcc (Deng et al., 2006; Hasbi et al., 2009; Perreault et al., 2010; Gangarossa et al., 2013; Frederick et al., 2015; Gagnon et al., 2017) and D1R/D2R complexes were detected by PLA *in situ* in the striatum of rodents and non-human primates (Perreault et al., 2016; Rico et al., 2017; Hasbi et al., 2018), even though there has been some controversy since the work form Frederick and co-workers showed D1R/D2R complexes were not detectable by using the same approach *in vivo* in mice within the fraction of MSN expressing both D1R and D2R receptors (Frederick et al., 2015). In heterologous systems, the formation of D1R/D2R complexes could lead to atypical signaling: instead of the canonical $G_{s/olf}$ and $G_{i/o}$ proteins, D1R/D2R heteromers would be able to recruit G_q protein, leading to PLC-mediated intracellular Ca^{2+} release (Perreault et al., 2014). It was argued that the D1R ligand SKF83959 preferentially recruits D1R/D2R heteromer-dependent Ca^{2+} signaling, due to alterations of the D1R binding pocket when in the heteromeric complex, supporting the idea of an allosteric modulation within the D1R/D2R heteromers (Hasbi et al., 2009, 2010; Verma et al., 2010; Perreault et al., 2014).

To target D1R/D2R heteromers, Hasbi et al. (2014) designed and interfering peptide, based on putative interaction sites between both receptors involving 2 adjacent Arginine in the D2R-IL3 and 2 adjacent Glutamic acid of the D1R CTD (O'Dowd et al., 2012). This “Tat-D1” peptide, corresponding to amino acid 396–413 of the D1R CTD, was shown to perturb i) D1R/D2R – but not D2R-D5R - interaction, ii) SKF83959-induced Ca^{2+} transients *in vitro* and iii) co-immunoprecipitation from membrane extracts, while a scrambled peptide had no effect (Hasbi et al., 2014).

In the context of addiction, the Tat-D1 peptide was shown to reverse the SKF83959-induced inhibition of amphetamine sensitization (Shen et al., 2015a). The same group showed that the Tat-D1 peptide alone enhanced cocaine-induced locomotor sensitization and place-preference, as well as the reinstatement after self-administration (Perreault et al., 2016; Hasbi et al., 2018). It should be noted that the Tat-D1 peptide displayed, by itself, pro-locomotor effects (Shen et al., 2015a) and induced place-preference (Perreault et al., 2016; Hasbi et al., 2018). Importantly, the Tat-D1 peptide used to disrupt D1R/D2R interaction strongly overlaps with the so-called “Tat-D1R-t2 peptide” originally designed to block D1R/NMDAR heteromers (Nai et al., 2010; Ladepeche et al., 2013; see section 3.1). Furthermore, the Tat-D1R-t2 was shown to induce, by itself, ERK activation (Cahill et al., 2014b) and to potentiate glutamatergic synapses (Ladepeche et al., 2013), suggesting that this peptide could mimic D1R/NMDA interaction (see section 3.1), which could explain the pro-rewarding effect of the Tat-D1 peptide used by the George's group. The specificity of the Tat-D1 peptide in selectively impairing D1R/D2R interaction has therefore to be further validated. Moreover, most of the *in vivo* effects of the Tat-D1 peptide were assessed through its ability to abolish/attenuate the behavioral impact of SKF83959 (Hasbi et al., 2014, 2018; Shen et al., 2015a,b). Yet, the properties of SKF83959 as a preferential ligand for D1R/D2R heteromers capable of recruiting G_q-dependent mechanisms has been recently challenged (Chun et al., 2013; Lee et al., 2014a,b; Frederick et al., 2015). Further work is needed to unravel the unique properties of this atypical subpopulation of MSN co-expressing both D1R and D2R and their potential regulation by putative D1R/D2R heteromers.

3. D1R heteromers and addiction

3.1. D1R/NMDA heteromers

As opposed to the inhibitory role of D2R on NMDAR currents (see section 2.3), there is a general consensus toward a facilitating effect of D1R stimulation on NMDAR functions (Flores-Hernandez et al., 2002; Wittmann et al., 2005; but see Lee et al., 2002). This positive feedback is bi-directional since NMDAR stimulation also favors D1R surface expression and downstream cAMP production (Pei et al., 2004). The mechanisms underlying the interplay between D1R and NMDAR signals have been intensely investigated, notably because targeting these processes offers the prospect of restoring the imbalance in D1R and NMDAR functions described in numerous psychiatric diseases (Cepeda and Levine, 2006; Missale et al., 2006; Yao et al., 2008; Wang et al., 2012).

The synergy between D1R and NMDAR plays functional roles in drug of abuse-mediated responses. We observed that psychostimulant-mediated striatal activation of ERK1/2, which controls long-term neuronal adaptations, relied on a concomitant stimulation of D1R and NMDAR (Valjent et al., 2000, 2005; Pascoli et al., 2011a). This convergence of DA and glutamate signals onto ERK1/2 involves a D1R-mediated phosphorylation of GluN2B-containing NMDAR on Tyr^{1472} via the tyrosine kinase Fyn, which triggers a Ca^{2+}-dependent activation of ERK1/2 that launches cocaine-induced epigenetic, genic, morphological and behavioral changes (Fig. 1d; Pascoli et al., 2011a). In addition to signaling cascades linking D1R stimulation to a facilitation of GluN2B-NMDAR, the potential role D1R/NMDAR heteromers in drug of abuse-evoked plasticity is only emerging.

The seminal work of Fang Liu and colleagues led to the identification of a direct binding of D1R, but not D5R, to the GluN1 and GluN2A subunits of NMDAR in cultured cells overexpressing the receptors, and hippocampal tissues (Lee et al., 2002; Pei et al., 2004). These D1R/GluN1 complexes were also detected in the mouse striatum (Cahill et al., 2014b), including in PSD fractions (Fiorentini et al., 2003), as well as in human post-mortem caudate putamen tissues (AA, ESJ, RW, PT, PV unpublished observations). *In vitro* assays showed that the D1R-t2 (L^{387}- L^{416}) and D1R-t3 (S^{417}-T^{446}) domains of D1R CTD bind to the CTD of GluN1 and GluN2 subunits, respectively (Fig. 1e–f; Lee et al., 2002). The D1R-t2 domain binds to the C1 cassette of GluN1 (GluN1-C1; D^{864}- T^{900}; Lee et al., 2002; Fiorentini et al., 2003; Pei et al., 2004), which comprises multiple PKA and PKC phosphorylation sites (Tingley et al., 1997; Wang et al., 2014) and controls NMDAR trafficking (Ehlers et al., 1995; Scott et al., 2003). Pull-down assays coupled to mass spectrometry established that electrostatic interactions between the Arginine-rich epitope localized in GluN1-C1 and the acidic residues in the D1R-t2 region mediate D1R/GluN1 interaction (Woods et al., 2005). These findings highlight the importance of epitope-epitope electrostatic interactions for both D1R/NMDA and D2R/A2AR (see section 2.1), suggesting that they might represent a general mechanism for receptor heteromerization. Of note, the D1R-t2 and GluN1-C1 amino acid sequences are conserved across species, supporting the hypothesis that D1R/NMDAR heteromers might be involved in physiological functions that have been preserved through evolution (Woods et al., 2005).

Studies on the modulation of D1R/GluN1 interaction by receptor agonists or antagonists led to controversial findings, with authors reporting a D1R agonist-dependent decrease of endogenous D1R/GluN1 heteromers in cultured hippocampal neurons (Lee et al., 2002), whereas BRET experiments performed on cell lines overexpressing the receptors showed no effect of D1R or NMDAR agonists and antagonists (Fiorentini et al., 2003).

To study whether cocaine could modulate endogenous D1R/GluN1 heteromerization, we first used cultured striatal neurons co-stimulated with a D1R agonist together with a low dose of glutamate, a model that we validated as instrumental to study cocaine-evoked signaling *in vivo* (Pascoli et al., 2011a; Cahill et al., 2014b). Notably, this co-stimulation paradigm, which induces a D1R-mediated facilitation of NMDAR as observed *in vivo* in response to cocaine, led to a significant increase of D1R/GluN1 heteromers (Cahill et al., 2014b). Their potential role in the convergence of D1R and NMDAR signals onto ERK1/2 activity was assessed with a cell-penetrating peptide corresponding to the C1 cassette of GluN1 (TAT-GluN1-C1; Fig. 1g). This peptide efficiently disrupted D1R/GluN1 heteromerization induced by the co-stimulation, as well as the D1R-mediated potentiation of Ca^{2+} transients through GluN2B-NMDAR and downstream ERK activation. Importantly, the TAT-GluN-C1 peptide was able to block the D1R/NMDAR-dependent signaling, while preserving the functions of individual D1R and NMDAR (Cahill et al., 2014b). The inhibition of D1R/GluN2A interaction with a TAT-D1R-t3 peptide had no effect on ERK1/2 activation downstream of D1R and NMDAR. These observations posit D1R/GluN1 heteromers as the molecular bridge linking DA to the facilitation of NMDAR and ERK activation in an *in vitro* model of cocaine exposure.

Since drug-induced adaptive behavior has been causally linked to long-term synaptic plasticity of glutamate synapses onto dMSN (Pascoli et al., 2011b, 2014b), it seems critical to determine whether D1R/NMDAR heteromers are present at synaptic sites and can control synaptic plasticity.

On organotypic striatal cultures the lateral diffusion of D1R at the plasma membrane is greatly reduced upon NMDAR stimulation, which favors confined D1R expression within dendritic spines. This recruitment of D1R in spines depends on D1R/GluN1 heteromer formation, leading to the model of 'diffusion trap system" whereby agonist-induced allosteric changes of NMDAR enhances D1R/NMDAR interaction at synaptic sites (Scott et al., 2006). This model stipulates that upon glutamate release, D1R/NMDAR heteromers are preferentially formed within, or at the close vicinity of, synapses. Accordingly, the CTD of both GluN2 subunits of NMDAR and D1R are known to bind the synaptic protein PSD-95, which stabilizes their localization at synapses (Kornau et al., 1995; Niethammer et al., 1996; Kim and Sheng, 2004; Zhang et al., 2009; Ladepeche et al., 2013). The expression of both receptors is thus confined at synaptic sites owing to their interaction with PSD-95. However, Zhang and colleagues demonstrated that GluN1 and PSD-95 bind to the D1R CTD through docking sites that overlap at the level of the D1R-t2 domain (Zhang et al., 2009). Through a competition mechanism, PSD-95 is thus a limiting factor for D1R/GluN1 heteromerization at synapses, even though these receptors complexes are detected in striatal PSD fractions (Fiorentini et al., 2003).

To assess the role of D1R/GluN1 interaction in the modulation of synaptic transmission, electrophysiological recordings were performed from cortico-striatal slices prepared from the *drd1a-egfp* reporter mice to visualize dMSN (Gong et al., 2003). Inhibition of D1R/NMDAR interaction with the GluN1-C1 peptide fully blocked D1R-mediated facilitation of NMDA-mediated excitatory post-synaptic currents, while sparing basal synaptic transmission (Cahill et al., 2014b). A GluN2B antagonist was also able to abrogate the D1R-mediated facilitation of NMDA currents, whereas disruption of D1R/GluN2A heteromers with the D1R-t3 peptide had no effect. This suggests that D1R/GluN2A heteromers are not primarily involved in the modulation of NMDAR currents by DA in dMSN. It also shows that D1R/GluN1 interaction preferentially modulates GluN2B-NMDAR, even though the underlying mechanism is still unknown.

To study the role of D1R/GluN1 interaction in striatal plasticity, high frequency electrical stimulations (HFS) of the cortex triggering long-term potentiation (LTP) of striatal synapses in both dMSN and iMSN were applied to cortico-striatal slices (Pascoli et al., 2011b). This allowed us to demonstrate the mandatory role of D1R/NMDAR heteromers for LTP in dMSN, but not iMSN (Cahill et al., 2014b). Accordingly, the facilitating effect of D1R on NMDAR-mediated LTP also required D1/NMDAR interaction in the hippocampus (Nai et al., 2010). In contrast, Ladepeche and co-workers found that blocking D1R/GluN1 interaction with the TAT-D1R-t2 peptide increased the number of potentiated synapses in a chemically-induced LTP in cultured hippocampal neurons (Ladepeche et al., 2013). The apparent discrepancy between these results is likely due to differences in experimental models (cortico-striatal slices v.s hippocampal neurons) and/or to the strategies used to block D1R/GluN1 heteromers. In fact, we found that the D1R-t2 peptide was able to activate NMDAR and ERK by itself (Cahill et al., 2014b), which could explain its permissive effect on chemical LTP. By contrast, when using the GluN1-C1 peptide, which disrupts D1R binding to NMDAR without affecting the functions of individual D1R and NMDAR, we observed a blockade of HFS-induced striatal LTP (see Andrianarivelo et al., 2018). Regarding cocaine-evoked responses *in vivo*, the infusion of the TAT-GluN1-C1 peptide into the NAcc was able to attenuate cocaine-induced ERK1/2 activation. Inhibiting D1R/GluN1heteromers in the NAcc did not impact neither the basal locomotion nor the acute hyperlocomotor response to a first injection. By contrast, the disruption of D1R/GluN1 interaction prior and during the first injection of cocaine altered the locomotor sensitization induced by a second injection of cocaine administered a week later (Cahill et al., 2014b). This supports a role for D1R/GluN1 heteromers in the NAcc in the development of persistent cocaine-induced adaptations in acute models of cocaine exposure. To date, the impact of acute or chronic exposure on endogenous D1R/GluN1 heteromerization *in vivo* in the striatum and in other brain structures of the reward circuit is still not known. Whether or not these heteromers are involved in the development and maintenance of long-lasting structural and behavioral adaptation remains to be established. We are currently tackling these issues, which are critical because they will unravel whether of D1R/GluN1 and D2R/GluN2 heteromers are mediators of the excitatory and inhibitory actions of drugs of abuse on dMSN and iMSN, respectively.

4. Conclusions and perspectives

Numerous studies focused on the mechanisms underlying allosteric changes induced receptor heteromerization and associated modification of downstream signaling but only few reports described roles of endogenous heteromers *in vivo* (Table 1). This is likely due to limitations of current approaches to detect heteromers *in situ*. In fact, class C GPCRs form stable oligomers but class A GPCRs oligomerization seems highly dynamic, and its existence is still a matter of debate. Furthermore, most discoveries on receptor oligomers originate from studies in heterologous systems lacking the dense synaptic macroproteic complexes where receptors have multiple and dynamic interactors. These interactions, sometimes involving overlapping sites, represent a major challenge to selectively alter heteromer formation without impacting on the component receptor's interaction with other partners. This implies a thorough characterization of potential off-target effects and caution when interpreting the results. Such strategy design could benefit from crystal structures of the receptors to model the interface of heteromers, as recently performed for D2R/A2R (Borroto-Escuela et al., 2018c). This could facilitate the identification of the minimal amino-acid residues necessary for receptor heteromerization, the design of non-peptidic interfering molecules or bi-valent compounds selectively targeting receptor oligomers (Soriano et al., 2009).

Several DA receptors heteromers with a therapeutic potential have been described, including D1R/D3R (Fiorentini et al., 2010), but their

roles remain to be established. Moreover, most studies on receptor heteromers in addiction focused on the striatum because of its key role in the pathology and its enrichment in DA receptors. However, a thorough characterization of heteromer expression within the entire brain reward circuit would be of importance considering the implication of various brain regions in distinct components of addiction. Moreover, the implication of DA receptor heteromers has been mainly studied in the initial phases of drug exposure. Addressing their roles in each phases of drug addiction (maintenance, craving and relapse) seems of crucial importance as it could open new routes for the development of selective strategies targeting these heteromers for the treatment of drug addiction.

Declaration of interest

The authors report not biomedical financial interest or conflicts of interest.

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