Dopamine signaling in reward-related behaviors

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Dopamine (DA) regulates emotional and motivational behavior through the mesolimbic dopaminergic pathway. Changes in DA mesolimbic neurotransmission have been found to modify behavioral responses to various environmental stimuli associated with reward behaviors. Psychostimulants, drugs of abuse, and natural reward such as food can cause substantial synaptic modifications to the mesolimbic DA system. Recent studies using optogenetics and DREADDs, together with neuron-specific or circuit-specific genetic manipulations have improved our understanding of DA signaling in the reward circuit, and provided a means to identify the neural substrates of complex behaviors such as drug addiction and eating disorders. This review focuses on the role of the DA system in drug addiction and food motivation, with an overview of the role of D1 and D2 receptors in the control of reward-associated behaviors.

Keywords: dopamine, dopamine receptor, drug addiction, food reward, reward circuit

INTRODUCTION

Dopamine (DA) is the predominant catecholamine neurotransmitter in the brain, and is synthesized by mesencephalic neurons in the substantia nigra (SN) and ventral tegmental area (VTA). DA neurons originate in these nuclei and project to the striatum, cortex, limbic system and hypothalamus. Through these pathways, DA affects many physiological functions, such as the control of coordinated movements and hormone secretion, as well as motivated and emotional behaviors (Hornykiewicz, 1966; Beaulieu and Gainetdinov, 2011; Trinch and Sabatini, 2012).

Regulation of the DA system in reward-related behaviors has received a great deal of attention because of the serious consequences of dysfunction in this circuit, such as drug addiction and food reward linked obesity, which are both major public health issues. It is now well accepted that following repeated exposure to addictive substances, adaptive changes occur at the molecular and cellular level in the DA mesolimbic pathway, which is responsible for regulating motivational behavior and for the organization of emotional and contextual behaviors (Nestler and Carlezon, 2006; Stuber and Kalivas, 2013). These modifications to the mesolimbic dopaminergic system lead to drug dependence, which is a chronic, relapsing disorder in which compulsive drug-seeking and drug-taking behaviors persist despite serious negative consequences (Thomas et al., 2008).

Recent findings suggest that glutamatergic and GABAergic synaptic networks in the limbic system are also affected by drugs of abuse, and that this can alter the behavioral effects of addictive drugs (Schmidt and Pierce, 2010; Lüscher and Malenka, 2011). Considerable evidence now suggests that substantial synaptic modifications of the mesolimbic DA system are associated with not only the rewarding effects of psychostimulants and other drugs of abuse, but also with the rewarding effects of natural reward, such as food; however, the mechanism by which drugs of abuse induce the modify synaptic strength in this circuit remains elusive. In fact, DA reward signaling seems extremely complex, and is also implicated in learning and conditioning processes, as evidenced by studies revealing a DAergic response coding a prediction error in behavioral learning, for example (Wise, 2004; Schultz, 2007, 2012), thus suggesting a need for a fine dissection at a circuit level to properly understand these motivated reward-related behaviors. Recent studies using optogenetics and neuron-specific or circuit-specific genetic manipulations are now allowing a better understanding of DA signaling in the reward circuit.

In this review, I will provide a short summary of DA signaling in reward-related behaviors, with an overview of recent studies on cocaine-addiction behaviors as well as some on food reward in the context of the role of D1 and D2 receptors in regulating these behaviors.

DOPAMINE RECEPTORS

Dopamine interacts with membrane receptors belonging to the family of seven transmembrane domain G-protein coupled receptors, with activation leading to the formation of second messengers, and the activation or repression of specific signaling pathways. To date, five different subtypes of DA receptors have been cloned from different species. Based on their structural and pharmacological properties, a general subdivision into two groups has been made: the D1-like receptors, which stimulate intracellular cAMP levels, comprising D1 (Dzirayry et al., 1990; Zhou et al., 1990) and D5 (Grandy et al., 1991; Sunahara et al., 1991), and the D2-like receptors, which inhibit intracellular cAMP levels, comprising D2 (Bruno and et al., 1989; Dal Toso et al., 1989), D3 (Sokoloff et al., 1990), and D4 (Van Tol et al., 1991) receptors.

D1 and D2 receptors are the most abundantly expressed DA receptors in the brain. The D2 receptor has two isoforms generated by alternative splicing of the same gene (Dal Toso et al., 1989; Montmayeur et al., 1991). These isoforms, named D2L and D2S, are identical except for an insert of 29 amino acids present in the putative third intracellular loop of D2L, an intracellular domain thought to play a role in coupling this class of receptor to specific second messengers.
D2 receptors are localized presynaptically, revealed by D2 receptor immunoreactivity, mRNA, and binding sites present in DA neurons throughout the midbrain (Drewe et al., 1994), with lower level of D2 receptor expression in the VTA than in the SN (Haber et al., 1993). These D2-type autoreceptors represent either somatodendritic autoreceptors, known to dampen neuronal excitability (Lacey et al., 1987, 1988; Chaudo and Kapatos, 1992), or terminal autoreceptors, which mostly decrease DA synthesis and packaging (Onali et al., 1988; Pothis et al., 1998), but also inhibit impulse-dependent DA release (Cass and Zahnisser, 1991; Kennedy et al., 1992; Conger et al., 2002). Therefore, the principal role of these autoreceptors is the inhibition and modulation of overall DA neurotransmission; however, it has been suggested that in the embryonic stage, the D2-type autoreceptor could have a different function in DA neuronal development (Kim et al., 2006, 2009; Yoon et al., 2011; Yoon and Baik, 2013). Thus, the cellular and molecular role of these presynaptic D2 receptors needs to be explored further. The expression of D3, D4, and D5 receptors in the brain is considerably more restricted and weaker than that of either D1 or D2 receptors.

There is some difference in the affinity of DA for D1-like receptors and D2-like receptors, mostly reported on the basis of receptor-ligand binding assays using heterologously expressed DA receptors in cell lines. For example, D2-like receptors seem to have a 10- to 100-fold greater affinity for DA than the D1-like family, with the D1 receptor reported to have the lowest affinity for DA (Beaulieu and Gainetdinov, 2011; Tritsch and Sabatini, 2012). These differences suggest a differential role for the two receptors given that DA neurons can have two different patterns of DA release, “tonic” or “phasic” based on their firing properties (Grace et al., 2007). It has been suggested that low-frequency, irregular firing of DA neurons tonically generates a low basal level of extracellular DA (Grace et al., 2007), while burst firing, or “phasic” activity is crucially dependent on afferent input, and is believed to be the functionally relevant signal sent to postsynaptic sites to indicate reward and modulate goal-directed behavior (Berridge and Robinson, 1998; Schultz, 1998; Girault, 2012).

In the case of D2 receptors, the situation is further complicated, as D2 receptors are alternatively spliced, giving rise to isoforms with distinct physiological properties and subcellular localizations. The large isoform appears to be expressed dominantly in all brain regions, although the exact ratio of the two isoforms can vary (Montminy et al., 1991). In fact, the phenotype of D2 receptor total knockoutKO mice was found to be quite different from that of D2L KO mice (Baik et al., 1993; Usiel et al., 2000), indicating that the two isoforms might have different functions in signaling pathways mediated by D1 and D2 receptors.

The D1- and D2-like receptor classes differ functionally in the intracellular signaling pathways they modulate. The D1-like receptors, including D1 and D5, are coupled to heterotrimERIC G-proteins that include the G proteins Gαi and Gαq, with activation leading to increased adenyl cyclase (AC) activity, and increased cyclic adenosine monophosphate (cAMP) production. This pathway induces the activation of protein kinase A (PKA), resulting in the phosphorylation of variable substrates and the induction of immediate early gene expression, as well as the modulation of numerous ion channels. In contrast, D2-class DA receptors (D2, D3, and D4) are coupled to Gαs and Gαo proteins, and negatively regulate the production of cAMP, resulting in decreased PKA activity, activation of K+ channels, and the modulation of numerous other ion channels (Kebabian and Greengard, 1981; Beaulieu and Gainetdinov, 2011).

One of best-studied substrates of PKA is the DA- and cAMP-regulated phosphoprotein, Mr ∼32,000 (DARPP-32), which is an inhibitor of protein phosphatase, and is predominantly expressed in medium spiny neurons (MSNs) of the striatum (Hemmings et al., 1984a). It appears that DARPP-32 acts as an integrator involved in the modulation of cell signaling in response to DA in striatal neurons. It has been demonstrated that phosphorylation of DARPP-32 at threonine 34 by PKA activates inhibitory function of DARPP-32 over the protein phosphatase (PP1; Hemmings et al., 1984a,b). In D1 receptor expressing striatal neurons, D1 receptor stimulation results in an increased phosphorylation of DARPP-32 in response to PKA activation, while stimulation of D2 receptors in D2 receptor-expressing neurons reduces the phosphorylation of DARPP-32 at threonine 34, presumably as a consequence of reduced PKA activation (Batuec et al., 2008). However, it appears that a cAMP-independent pathway also participates in the D2-receptor-mediated regulation of DARPP-32, given that dephosphorylation of threonine 34 by the calcineurin-dependent protein phosphatase 2B (PP2B; also known as calcineurin), which is activated by increased intracellular Ca2+, following D2 receptor activation (Nishi et al., 1997). These findings suggest that DA exerts a bidirectional control on the state of phosphorylation of DARPP-32, a DA-centered signaling molecule. Therefore, one can imagine that overall, under DA tone, these signaling pathways mediated by the two classes of receptors can influence neuronal excitability, and consequently synaptic plasticity, in terms of their synaptic networks in the brain, given that their precise signaling varies depending on the cell type and brain region in which they are expressed (Beaulieu and Gainetdinov, 2011; Gainetdinov, 2012).

In the case of D2 receptors, the situation is further complicated, as D2 receptors are alternatively spliced, giving rise to isoforms with distinct physiological properties and subcellular localizations.
DA receptor-mediated ERK activation involves interaction with the NMDA glutamate receptor (see text), which is expressed predominantly in the striatum. The stimulation of D1 receptors is not able to mediate ERK phosphorylation per se, but rather requires endogenous glutamate (Pascoli et al., 2011). Stimulation of D1 receptors increases calcium influx through NMDA receptors, which involves phosphorylation of the NMDA receptor NR2B subunit by a Src-family tyrosine kinase (Pascoli et al., 2011). This increased calcium influx activates a number of signaling pathways, including calcium and calmodulin-dependent kinase II (CamKII), which can activate ERK via the Ras-Raf-MEK cascade (Fasano et al., 2009; Shiflett and Balaban, 2011; Girault, 2012). Upon D1 receptor activation, activated PKA can mediate phosphorylation of DARPP-32 and phosphorylated DARPP-32 can act as potent inhibitor of the protein phosphatase (PP-1), which dephosphorylates another phosphatase, the striatal-enriched tyrosine phosphatase (STEP). Dephosphorylation of STEP activates its phosphatase activity, thus allowing STEP to dephosphorylate ERK. DARPP-32 also acts upstream of ERK, possibly by inhibiting PP-1 from dephosphorylating MEK, the upstream kinase of ERK. Thus, D1 receptor activation increases ERK phosphorylation by preventing its dephosphorylation by STEP but also by preventing the dephosphorylation of the upstream kinase of ERK. In addition, the cross talk between D1 and NMDA receptors contributes to the ERK activation. For example, a recent study showed that stimulation of D1 receptors increases calcium influx through NMDA receptors, a process that involves phosphorylation of the NMDA receptor NR2B subunit by a Src-family tyrosine kinase (Pascoli et al., 2011). This increased calcium influx activates a number of signaling pathways, including calcium and calmodulin-dependent kinase II, which can activate ERK via the Ras-Raf-MEK cascade (Fasano et al., 2009; Shiflett and Balaban, 2011; Girault, 2012). Consequently, D1 receptor-mediated ERK activation employs a complex regulation by phosphatases and kinases in addition to the cross talk with glutamate receptor signaling (Figure 1).
DA activates ERK signaling via mesencephalic D2 receptors, which, in turn, activate the transactivation of receptor tyrosine kinase (RTK), which consequently activates downstream signaling involving matrix metalloproteinases (MMPs) with ectodomain shedding of EGFR ligand, for example, to finally activate ERK (Choi et al., 1999; Kim et al., 2004; Wang et al., 2005; Yoon et al., 2011). The involvement of arrestin has also been suggested to contribute to D2 receptor-mediated ERK activation (Baum et al., 2004; Kim et al., 2004), which can activate MAPK signaling by mobilizing clathrin-mediated endocytosis in a β-arrestin-dependent manner (Kim et al., 2004). Thus, the physiological relevance of this D2 receptor-mediated ERK activation requires the contribution of neuroadaptation (Kalivas and Duffy, 1990; Robinson and Berridge, 1993). While this phenomenon has been studied mostly in experimental animals, the neuronal plasticity underlying behavioral sensitization is believed to reflect the neuroadaptations that contribute to compulsive drug cravings in humans (Robinson and Berridge, 1993; Kalivas et al., 2004). It has been suggested that the mesolimbic DA system from the VTA to the nucleus accumbens (NAc) and perfrontal cortex is an important mediator of these plastic changes, in association with the glutamatergic circuitry (Robinson and Berridge, 1993; Kalivas et al., 1998; Vanderschuren and Kalivas, 2000). Animals behaviorally sensitized to cocaine, amphetamine, nicotine, or morphine (Kalivas and Duffy, 1990; Parsons and Justice, 1993) show enhanced DA release in the NAc in response to drug exposure. In addition to changes in neurotransmitter release, DA binding to its receptors plays a key role in behavioral sensitization (Steketee and Kalivas, 2011). For example, the enhanced excitability of VTA DA neurons that occurs with repeated cocaine exposure is associated with decreased D2 autoreceptor sensitivity (White and Wang, 1984; Henry et al., 1989). In addition, repeated intra-VTA injections of low doses of the D2 antagonist eticlopride, which is presumably autoreceptor-selective, enhanced subsequent responses to amphetamine (Tanabe et al., 2004).

A number of studies have shown that D1 and D2 DA receptors are differentially involved in cocaine-induced changes in locomotor activity. For example, initial studies employing pharmacological approaches have shown that mice or rats pre-treated...
Table 1 | Role of dopamine D1 and D2 receptors in cocaine-induced behaviors.

| Cocaine-induced behaviors          | Receptor-type | Animal models                                                                 | Effects mediated by cocaine                                      | Reference                                                                 |
|------------------------------------|---------------|-------------------------------------------------------------------------------|-----------------------------------------------------------------|--------------------------------------------------------------------------|
| **Cocaine-induced locomotor activity** |               |                                                                               |                                                                  |                                                                          |
| Cocaine-induced locomotor activity | D1            | D1 antagonist SCH23390                                                        | Diminished locomotor response to cocaine                        | Cabib et al. (1991), Ushijima et al. (1995), Hummel and                  |
|                                   | D1            | D1 KO mice                                                                   | Diminished locomotor response                                   | Unterwald (2002)                                                        |
|                                   | D1            | Loss of DARPP-32 in D1 cell, using DARPP-32 flox mice x D1-Cre mice           | Diminished acute locomotor response to cocaine                  | Xu et al. (1994)                                                        |
|                                   | D2            | D2 antagonist Haloperidol, raclopride                                         | Unaffected                                                      | Cabib et al. (1991), Ushijima et al. (1995)                              |
|                                   | D2            | D2 KO mice                                                                   | Increased but low level                                          | Chausmer et al. (2002), Welter et al. (2007), Sim et al. (2013)        |
|                                   | D2            | Loss of DARPP-32 in D2 cell, using DARPP-32 flox mice x D2-Cre mice           | Increased acute locomotor response to cocaine                   | Unterwald (2010)                                                        |
|                                   | D1            | D1 antagonist SCH23390 (i.p or VTA)                                           | Unaffected                                                      | Kuribara and Uchihashi (1993), Mattingly et al. (1994),                 |
|                                   | D1            | D1 KO mice                                                                   | Not fully prevent cocaine sensitization at all doses             | Karlsson et al. (2008)                                                  |
|                                   | D1            | Optogenetically activated with Conditional ChR2 viruses injected in NAc of D1-Cre mice | Enhanced cocaine sensitization                                  | Lobo (2010)                                                             |
|                                   | D1            | Inhibition of D1 cell with Tetanus toxin light chain expression in D1-MSN      | Diminished cocaine sensitization                                  | Hikida et al. (2010)                                                    |
|                                   | D1            | Optogenetic inactivation of D1-MSN cells with halorhodopsin                  | Diminished cocaine sensitization                                  | Chandra et al. (2013)                                                   |
|                                   | D1            | Reconstruction of D1 expression in NAc of D1 KO mice                         | Mediate D1-independent cocaine sensitization                     | Gore and Zweifel (2013)                                                 |
|                                   | D2            | D2 antagonist sulpiride, YM-09151-2, eticlopride                             | Unaffected                                                      | Kuribara and Uchihashi (1993), Martinley et al. (1994),                 |
|                                   | D2            | D2 antagonist quinpirole in intra medial prefrontal cortex                    | Blunted cocaine sensitization                                    | Beyer and Steketee (2002)                                               |
|                                   | D2            | D2 KO mice                                                                   | Unaffected                                                      | Sim et al. (2003)                                                       |
|                                   | D2            | Depletion of D2 receptors in the NAc by shRNA delivery                       | Unaffected                                                      | Sim et al. (2013)                                                       |
|                                   | D2            | Optogenetically activated with Conditional ChR2 viruses injected in NAc of D2-Cre mice | Unaffected                                                      | Lobo (2010)                                                             |
|                                   | D2            | Inhibition of D2 cell with Tetanus toxin light chain expression in D2-MSN      | Slightly decreased cocaine sensitization                        | Hikida et al. (2010)                                                    |
| Cocaine-induced behaviors | Receptor-type | Animal models | Effects mediated by cocaine | Reference |
|---------------------------|--------------|---------------|----------------------------|-----------|
| CPP                       | D1 system    | Diminished cocaine CPP | Cervo and Samanin (1995), Baker et al. (1998) |
| D1 KO mice                |              | Normal CPP | Miner et al. 0:959, Karasinska et al. (2009) |
| D1 optogenetically        |              | Enhanced cocaine CPP | Lobo (2010) |
| D1 inhibition of D1 cell  |              | Diminished cocaine CPP | Hikida et al. (2010) |
| D2 systemic administration|              | Normal CPP | Spyrali et al. (1982), Cervo and Samanin (1995), Shippenberg and Heidbreder (1995), Naazin et al. (2004) |
| D2 KO mice                |              | Normal CPP | Welter et al. (2007), Sim et al. (2013) |
| D2 depletion of D2 receptors in NAc by shRNA delivery |              | Normal CPP | Sim et al. (2013) |
| D2 optogenetically        |              | Diminished cocaine CPP | Lobo (2010) |
| D2 inhibition of D2 cell  |              | No change in CPP | Hikida et al. (2010) |
| D2 Conditional KO of D2 autoreceptors |              | Enhanced cocaine CPP | Bello et al. (2011) |
| Cocaine self-administration and cocaine-seeking behaviors | D1 antagonist | Dose-dependent biphasic effect in self-administration | Woolerton (1986), Britton et al. (1991), Hubner and Moreton (1991), Vanover et al. (1991), Caine and Koob (1994) |
| D1 agonist                |              | No effect in reinstatement of cocaine-seeking behavior | Self et al. (1995), De Vries et al. 0:995, Spealman et al. (1991), Khroyan et al. (2000) |
| D1 KO mice                |              | Diminished cocaine self-administration | Caine et al. (2007) |
| D2 antagonist              |              | Dose-dependent biphasic effect in self-administration | Woolerton (1986), Britton et al. (1991), Hubner and Moreton (1991), Caine and Koob (1994) |
| D2 agonist                |              | Induce reinstatement of cocaine-seeking behavior | Self et al. (1996), De Vries et al. 0:995, 2002, Spealman et al. (1999), Khroyan et al. (2000), Fuchs et al. (2002) |
| D2 KO mice                |              | Increased cocaine self-administration | Caine et al. (2002) |
| D2 KO mice                |              | With stress, reinstatement of cocaine-seeking behavior is attenuated | Sim et al. (2013) |
| D2 optogenetic activation of D2-MSNs in NAc |              | Suppress cocaine self-administration | Bock et al. (2013) |
with the D1 receptor antagonist SCH 23390 showed an attenuated locomotor response to acute cocaine challenge, while the D2 receptor antagonists haloperidol, and raclopride had no such effect (Cabib et al., 1991; Usui et al., 1993; Hummel and Unterrüwel, 2002). These results suggest different roles of DA receptor subtypes in the modulation of the stimulant effects of cocaine on locomotion. However, with regards to the behavioral sensitization induced by repetitive injections of cocaine, it has been reported that systemic administration of the D1 receptor antagonist SCH23390, or of the D2 receptor antagonists sulpiride, YM-09151-2 or eticlopride, does not affect the induction of cocaine sensitization (Kuribara and Uchihashi, 1993; Mattingly et al., 1994; Steketee, 1998; White et al., 1999; Vanderschuren and Kalivas, 2000).

The effects of direct intra-accumbens administration of SCH23390 on cocaine-induced locomotion, sniffing, and conditioned place preference (CPP) were investigated in rats, and these studies showed that the stimulation of D1-like receptors in the NAc is necessary for cocaine-CPP, but not for cocaine-induced locomotion (Baker et al., 1998; Neisewander et al., 1998). The direct intra-accumbens infusion of the D2/D3 receptor antagonist sulpiride in rats demonstrated that blockade of D2 receptors reverses the acute cocaine-induced locomotion (Neisewander et al., 1995; Baker et al., 1996), but these studies did not examine the effect on cocaine-induced behavioral sensitization. Interestingly, it has been reported that injection of the D2 receptor agonist quinpirole into the intra-medial prefrontal cortex blocked the initiation and attenuated the expression of cocaine-induced behavioral sensitization (Beyr and Steketee, 2002).

D1 receptor null mice have been examined in the context of addictive behaviors, and initial studies revealed that D1 receptor mutant mice failed to exhibit the psychomotor stimulant effect of cocaine on motor and stereotyped behaviors compared to their wild-type littersmates (Xu et al., 1994; Drago et al., 1996). However, it appears that D1 receptor KO abolishes the acute locomotor response to cocaine, but does not fully prevent locomotor sensitization to cocaine at all doses (Karlsson et al., 2008), demonstrating that genetic KO of D1 receptors is not sufficient to fully block cocaine sensitization under all conditions.

In D2 receptor KO mice, with reduced general locomotor activity, the cocaine-induced motor activity level is low compared to WT mice, but these animals were similar in terms of the ability to induce cocaine-mediated behavioral sensitization, or cocaine-seeking behaviors with a slight decrease in sensitivity (Chausmer et al., 2002; Weber et al., 2007; Sim et al., 2013). Depletion of D2 receptors in the NAc by infusion of a lentiviral vector with a shRNA against the D2 receptor did not affect basal locomotor activity, nor cocaine-induced behavioral sensitization, but conferred stress-induced inhibition of the expression of cocaine-induced behavioral sensitization (Sim et al., 2013). These findings, together with previous reports, strongly suggest that blockade of D2 receptors in the NAc does not prevent cocaine-mediated behavioral sensitization, and that D2 receptor in the NAc play a distinct role in the regulation of synaptic modification triggered by stress and drug addiction.

Recent studies using genetically engineered mice that express Cre recombinase in cell-type specific manner, revealed some role of D1 or D2 receptor-expressing MSNs in cocaine-addictive behaviors. For example, loss of DARPP-32 in D2 receptor-expressing cells resulted in an enhanced acute locomotor response to cocaine (Battep, 2010). Hikida and co-workers used AAV vectors to express tetra-cycline-repressive transcription factor (Tta) using substance P (for D1-expressing MSNs) or enkephalin (for D2-expressing MSNs) promoters (Hikida et al., 2010). These vectors were injected into the NAc of mice, in which tetanus toxin light chain (TN) was controlled by the tetracycline-responsive element, to selectively abolish synaptic transmission in each MSN subtype. Reversible inactivation of D1/D2 receptor-expressing MSNs with the tetanus toxin (Hikida et al., 2010) revealed the predominant roles of the D1 receptor-expressing cells in reward learning and cocaine sensitization, but there was no change in sensitization caused by the inactivation of D2 receptor-expressing cells. Using DREADD (designer receptors exclusively activated by a designer drugs) strategies, with viral-mediated expression of an engineered GPCR (Gs coupled human muscarinic M4DREADD receptor, hM4D) that is activated by an otherwise pharmacologically inert ligand, Ferguson et al. (2011) shown that the activation of striatal D2 receptor-expressing neurons facilitated the development of amphetamine-induced sensitization. However, the optogenetic activation of D2 receptor-expressing cells in the NAc induced no change in cocaine-induced behavioral sensitization (Lobo, 2010).

Optogenetic inactivation of D1 receptor-expressing MSNs using the light activated chloride pump, halorhodopsin eNpHR3.0 (enhanced Natronomonas pharaonis halorhodopsin 3.0), during cocaine exposure resulted in an attenuation of cocaine-induced locomotor sensitization (Chandra et al., 2013). Furthermore, the conditional reconstruction of functional D1 receptor signaling in subregions of the NAc in D1 receptor KO mice resulted in D1 receptor expression in the core region of the NAc, but not the shell, mediated D1 receptor-dependent cocaine sensitization (Goore and Zweifel, 2013). These findings suggest that DA mechanisms critically mediate cocaine-induced behavioral sensitization, with distinct roles for D1 and D2 receptors, although the precise contribution of D1 and D2 receptors and their downstream signaling pathways remains to be determined.
et al., 2004). Consistent with these pharmacological studies, D2 receptor KO mice displayed a comparable CPP score to WT mice (Welter et al., 2007; Sim et al., 2013). Furthermore, D2L−/− mice developed a CPP to cocaine as did WT mice (Smith et al., 2002).

Recently, the effect of a conditional presynaptic KO of D2 receptors on addictive behaviors has been reported, and this study demonstrated that mice lacking D2 autoreceptors displayed cocaine supersensitivity, exhibited increased place preference for cocaine, as well as enhanced motivation for food reward, perhaps owing to the absence of presynaptic inhibition by autoreceptors that further elevates extracellular DA and maximizes the stimulation of postsynaptic DA receptors (Bello et al., 2011). Results obtained from a different line of investigation showed that when D1-expressing MSNs are selectively activated by optogenetics, D1-Cre mice expressing DIO-AAV-ChR2-EYFP in the NAc displayed a significant increase in cocaine/blue-light preference compared to the control group (Lobo, 2010). In contrast, D2-Cre mice expressing DIO-AAV-ChR2-EYFP exhibited a significant attenuation of cocaine/blue-light preference relative to controls (Lobo, 2010), implicating a role for the activation of D1-expressing MSNs in enhancing the rewarding effects of cocaine, with activation of D2-expressing MSNs antagonizing the cocaine reward effect. Inhibition of D1-expressing MSNs with the tetanus toxin (Hikida et al., 2010) resulted in a diminished cocaine CPP, while no alterations to cocaine CPP after abolishing synaptic transmission in D2-expressing MSNs were observed (Hikida et al., 2010). Therefore, these data using optogenetics and cell-type specific inactivation of neurons implicate opposing roles of D1- and D2-expressing MSNs in CPP, with D1 receptor-expressing MSNs implicated in promoting both reward responses to psychostimulants, and D2 receptor-expressing MSNs dampening these behaviors (Lobo and Nestler, 2011).

**COCAINE SELF-ADMINISTRATION AND COCAINE-SEEKING BEHAVIORS**

Cocaine self-administration is an operant model in which laboratory animals lever press (or nose poke) for drug injections. The "self-administration" behavioral paradigm serves as an animal behavioral model of the human pathology of addiction (Thomas et al., 2008). It has been reported that selective lesion of DA terminals with 6-hydroxy DA (6-OHDA), or with the neurotoxin kainic acid in the NAc significantly attenuates cocaine self-administration, supporting the hypothesis that the reinforcers involved in reward, including the NAc, hippocampus, amygdala and/or pre-frontal cortex and midbrain (Palmiter, 2007; Kenny, 2008). Food and food-related cues can activate different brain circuits involved in reward, including the NAc, hippocampus, amygdala and/or pre-frontal cortex and midbrain (Palminter, 2007; Kenny, 2008). It is believed that the mesolimbic DA system promotes the learning of associations between natural reward and the environment in which they are found; thus, food, water, or cues
that predict them, promote rapid firing of DA neurons, and facilitate behaviors directed toward acquisition of the reward (Palmiter, 2007). Indeed DA-deficient mice show a loss of motivation to feed (Zhou and Palmiter, 1995), while D1 receptor null mice exhibit retarded growth and low survival after weaning; this phenotype can be rescued by providing KO mice with easy access to a palatable food, suggesting that the absence of D1 receptor is more related to a motor deficit (Drago et al., 1994; Xu et al., 1994). In contrast, D2 receptor KO mice show reduced food intake and body weight along with an increased basal energy expenditure level compared to their wild type littermates (Kim et al., 2010). Therefore, it is difficult to delineate the exact role of the DA system and of the receptor subtypes in food reward. Nevertheless, most human studies indicate the importance of the D2 receptor in the regulation of food reward in association with obesity.

**D2 Receptor Expression in Food Reward**

Increasing evidence suggests that variations in DA receptors and DA release play a role in overeating and obesity, especially in association with striatal D2 receptor function and expression (Sicte et al., 2011; Salamone and Correa, 2013). In animal studies, it has been shown that feeding increases the extracellular DA concentration in the NAc (Bassareo and Di Chiara, 1997), in a similar manner to drugs of abuse. However, in contrast to its effect on behaviors related to drug addiction, NAc DA depletion alone does not alter feeding behavior (Salamone et al., 1993). It appears that the pharmacological blockade of D1 and D2 receptors in the NAc affects motor behavior, amount and duration of feeding, but it does not reduce the amount of food consumed (Baldo et al., 2002). Interestingly, recent data showed that binge eating was ameliorated by the acute administration of unilateral NAc shell deep brain stimulation, and this effect was mediated in part by activation of the D2 receptor, while deep brain stimulation of the dorsal striatum had no influence on this behavior (Halpern et al., 2013) in mice. However, it has been reported that when exposed to the same high-fat diet, mice with a lower density of D2 receptors in the putamen exhibit more weight gain than mice with a higher density of D2 receptors in the same region (Huang et al., 2006). This study compared DAT and D2 receptor densities in chronic, high-fat diet-induced obese, obese-resistant and low-fat-fed control mice, and found that D2 receptor density was significantly lower in the rostral part of caudate putamen in chronic high-fat diet-induced obese mice compared to obese-resistant and low-fat-fed control mice (Huang et al., 2006). This low level of D2 receptor may be associated with altered DA release, and has also been reported that consumption of a high-fat, high-sugar diet leads to the downregulation of D2 receptors (Small et al., 2003) and reduced DA turnover (Davis et al., 2008).

In human studies, obese people and drug addicts both tend to show reduced expression of D2 receptors in striatal areas, and imaging studies have demonstrated that similar brain areas are activated by food- and drug-related cues (Wang et al., 2009). Positron emission tomography (PET) studies suggest that the availability of D2 receptors was decreased in obese individuals in proportion to their body mass index (Wang et al., 2001), thus suggesting that DA deficiency in obese individuals may perpetuate pathological eating as a means of compensating for the decreased activation of DA-mediated reward circuits. Volkow and co-workers also reported that obese versus lean adults show less striatal D2 receptor binding, and that this was positively correlated with metabolism in the dorsolateral prefrontal, medial orbitofrontal, anterior cingulate gyrus and somatosensory cortices (Volkow et al., 2008). This observation led to a discussion over whether decreases in striatal D2 receptors could contribute to overeating via the modulation of striatal prefrontal pathways that participate in inhibitory control and salience attribution, and whether the association between striatal D2 receptors and metabolism in the somatosensory cortices (regions that process palatability) could underlie one of the mechanisms through which DA regulates the reinforcing properties of food (Volkow et al., 2008).

Sicte and co-workers used functional magnetic resonance imaging (fMRI) to show that individuals may overeat to compensate for a hyperfunctioning dorsal striatum, particularly those with genetic polymorphisms of an A1 allele of the Taq1A in D2 receptor (DRD2/ANKK1) gene, which is associated with lower striatal D2 receptor density and attenuated striatal DA signaling (Sicte et al., 2008a,b). These observations indicate that individuals who show blunted striatal activation during food intake are at risk for obesity, particularly those also at genetic risk for compromised DA signaling in brain regions implicated in food reward (Sicte et al., 2008a,b). However, recent data showed that obese adults with or without binge eating disorder had a distinct genetic polymorphism of the Taq1A D2 receptor (DRD2/ANKK1) gene (Davis et al., 2012); therefore, it is plausible that similar brain DA systems are disrupted in both food motivation and drug addiction, even though it is not yet clear what these DA receptor data represent from the functional perspective of DA neurotransmission in brain.

As in obese people, low D2 receptor availability is associated with chronic cocaine abuse in humans (Volkow et al., 1993; Martinez et al., 2004). In contrast, overexpression of D2 receptors reduces the self-administration of alcohol in rats (Thanos et al., 2001). In humans, a higher-than-normal D2 receptor availability in non-alcoholic members of alcoholic families was reported (Volkow et al., 2006; Corsoed et al., 2012), supporting the hypothesis that low levels of D2 receptors may be associated with an increased risk of addictive disorders. Therefore, it is possible that in the brains of both obese individuals and chronic drug abusers, there are low basal DA concentrations, and periodic exaggerated DA release associated with either food or drug intake, along with low expression, or dysfunctional D2 receptors.

Dopamine receptor expression levels in other areas of the brain may also be important. For example, Fettissov et al. (2002) observed that obese Zucker rats, which display a feeding pattern consisting of large meal size and small meal number, have a comparatively low level of D2 receptor expression in the ventromedial hypothalamus (VMH). Interestingly, in their study, when a selective D2 receptor antagonist, sulpiride was injected into the VMH of obese and lean rats, a hyperphagic response was elicited only in the obese rats, suggesting that by aggravating the already low level of D2 receptors, it was possible to increase food intake. This low D2 receptor expression may cause an exaggerated DA release in obese rats during food ingestion and a reduced satiety feedback effect of DA, which would facilitate DA release into the brain areas “craving” for DA (Fettissov et al., 2002).
Recently, in an elegant study conducted by Johnson and Kenny (2010), it was observed that animals provided with a “cafeteria diet” consisting of a selection of highly palatable energy-dense food gained weight, demonstrating compulsive eating behavior. In addition to their excessive adiposity and compulsive-like eating, cafeteria diet rats also had decreased D2 receptor expression in the striatum. Surprisingly, lentivirus-mediated knockdown of striatal D2 receptors rapidly accelerated the development of addiction-like reward deficits, and the onset of compulsive-like food-seeking behavior in rats with extended access to palatable high-fat food (Johnson and Kenny, 2010), again indicating that common hedonic mechanisms may therefore underlie obesity and drug addiction. However, our own laboratory found somewhat unexpected results showing that D2 KO mice have a lean phenotype with enhanced hypothalamic leptin signaling compared to WT mice (Kim et al., 2010). Therefore, we cannot rule out that the D2 receptor plays a role in the homeostatic regulation of metabolism in association with a regulator of energy homeostasis such as leptin, in addition to its role in food motivation behavior. An animal model with a genetically manipulated conditional restriction of the D2 receptor in leptin receptor-expressing cells for example, or other reward-related neuronal cells, together with neural integrative tools, could potentially elucidate the role of the DA system via D2 receptors in food reward and the homeostatic regulation of food intake.

### DOPAMINERGIC REWARD SIGNALING LINKED TO HOMEOSTATIC FEEDING CIRCUIT

Increasing evidence indicates that homeostatic regulators of food intake, such as leptin, insulin, and ghrelin, control and interact with the reward circuit of food intake, and thus regulate behavioral aspects of food intake and conditioning to food stimuli behaviors (Abizaid et al., 2006; Fulton et al., 2006; Hommel et al., 2006; Baicy et al., 2007; Farooqi et al., 2007; Fulton et al., 2007; Konner et al., 2011; Volkow et al., 2011). Recent findings reveal that hormones implicated in regulating energy homeostasis also impinge directly on DA neurons; for example, leptin and insulin directly inhibit DA neurons, while ghrelin activates them (Palmiter, 2007; Kenny, 2011)

Hommel and co-workers demonstrated that VTA DA neurons express leptin receptor mRNA, and respond to leptin with inhibition and satiety (the prefrontal cortex; Baicy et al., 2007). Another peptide hormone, ghrelin, which is produced in the stomach and pancreas, is known to increase appetite and food intake (Abizaid et al., 2000). The ghrelin receptor growth hormone secretagogue 1 receptor (GHSR) is present in hypothalamic centers as well as in the VTA. Abizaid and co-workers showed that in mice and rats, ghrelin bound to neurons of the VTA, where it triggered increased DA neuronal activity, synapse formation, and DA turnover in the NAc, in a GHSR-dependent manner. In addition, they demonstrated that direct VTA administration of ghrelin also triggered feeding behavior, while intra-VTA delivery of a selective GHSR antagonist blocked the orexigenic effect of circulating ghrelin.
ghrelin, and blunted rebound feeding following fasting, suggesting that the DA reward circuitry is targeted by ghrelin to influence motivation for food (Abuad et al., 2006).

Insulin, which is one of the key hormones involved in the regulation of glucose metabolism, and inhibits feeding, has been shown to also regulate the DA system in the brain. Insulin receptors are expressed in brain regions that are rich in DA neurons, such as the striatum and midbrain (Zahniser et al., 1984; Figlewicz et al., 2003), suggesting a functional interaction between the insulin and DA systems. Indeed, it has been shown that insulin acts on DA neurons, and infusion of insulin into the VTA decreases food intake in rats (Figlewicz et al., 2008; Bruijnizel et al., 2011). Recent studies on the selective deletion of insulin receptors in midbrain DA neurons in mice demonstrated that this manipulation results in increased body weight, increased fat mass, and hyperphagia (Koner et al., 2011). While insulin acutely stimulated firing frequency in 50% of dopaminergic VTA/SN neurons, this response was abolished in those mice with the insulin receptor selectively deleted in DA neurons. Interestingly, in these mice, D2 receptor expression in the VTA was decreased compared to control mice. Moreover, these mice exhibited an altered response to cocaine under food-restricted conditions (Koner et al., 2011). Another recent report indicates that insulin can induce long-term depres- sion (LTD) of mouse excitatory synapses onto VTA DA neurons (Labouèbe et al., 2013). Furthermore, after a sweetened high-fat meal, which elevates endogenous insulin levels, insulin-induced LTD is occluded. Finally, insulin in the VTA reduces food anticipa- tory behavior in mice, and CPP for food in rats. This study raises an interesting issue about how insulin can modulate reward circuitry, and suggests a new type of insulin-induced synaptic plasticity on VTA DA neurons (Labouèbe et al., 2013).

CONCLUSIONS AND FUTURE DIRECTIONS

This review has focused on the role of the DA system, mainly con- centrating on the roles of D1 and D2 receptors in reward-related behaviors, including addiction and food motivation. However, it is well known that the DA system in this reward-circuit is finely mod- ulation by glutamatergic, GABAergic, and other neurotransmitter systems, which form specific circuits to encode the neuronal cor- relates of behaviors. Recent breakthroughs in optogenetic tools to alter neuronal firing and function with light, as well as DREADDs, together with genetic manipulation of specific neuronal cells or circuits are now allowing us to refine our insight into reward circuits in animals, and the hedonic value of food intake. It is of no doubt that these lines of investigation have provided a founda- tion for future direction of our study in neuroscience of the DA system in these behaviors. Future studies could include enlarged manipulations of important signaling molecules, for example, sig- naling molecules implicated in the D1 and D2 receptor signaling cascades, to explore the impact of these molecules on the induc- tion and expression of specific reward behaviors. Given that these two receptors employ distinct signaling pathways, in terms of their respective G protein coupling, as well as in the activation of downstream signaling molecules such as ERK, the differential distribution of receptors, as well as of their downstream signaling molecules may result in a different type of physiological response. Addition- ally, with this conceptual and technical evolution of the DA system in behaviors, this research will have important implications in the clinical investigation of related neurological disorders and psychi- atric diseases. Therefore, our continuing efforts to identify and characterize the organization and modification of DA synaptic functions in both animals and humans will contribute to the elu-cidation of neural circuits underlying the pathophysiology of drug addiction and eating disorders.

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Dopamine receptors in addiction and food motivation

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Studies indicate that the ventral striatum plays a key role in the development of food addiction and obesity, with increased dopamine transmission being associated with increased food intake and weight gain. The mesolimbic dopamine system, which includes the ventral striatum, is thought to be involved in the rewarding and reinforcing properties of food and other addictive drugs. This system is believed to play a crucial role in the development of addiction and obesity, and interventions aimed at modulating dopamine transmission may have potential therapeutic applications.

Dopamine receptors are involved in the reward and reinforcing properties of food and other addictive drugs. The interaction between dopamine receptors and the mesolimbic dopamine system plays a critical role in the development of addiction and obesity. Understanding the mechanisms underlying this interaction is an important area of research and has implications for developing effective treatments for these conditions.
Conflict of Interest Statement: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.