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ABSTRACT

Among the neurotransmitters involved in addiction, dopamine (DA) is clearly the best known. The critical role of DA in addiction is supported by converging evidence that has been accumulated in the last forty years. In the present review, firstly we describe the dopaminergic system in terms of connectivity, functioning and involvement in reward processes. Secondly, we describe the functional, structural, and molecular changes induced by drugs within the DA system in terms of neuronal activity, synaptic plasticity and transcriptional and molecular adaptations. Thirdly, we describe how genetic mouse models have helped characterizing the role of DA in addiction. Fourthly, we describe the involvement of the DA system in the vulnerability to addiction and the interesting case of addiction DA replacement therapy in Parkinson's disease. Finally, we describe how the DA system has been targeted to treat patients suffering from addiction and the result obtained in clinical settings and we discuss how these different lines of evidence have been instrumental in shaping our understanding of the physiopathology of drug addiction.

Keywords: substance abuse, reward, neuroplasticity, treatment, substantia nigra, VTA, striatum

Introduction

The involvement of dopamine (DA) in addiction processes has been proposed more than 40 years ago (Dackis and Gold 1985; Yokel and Wise 1975). Indeed, several converging anatomical, neurochemical, functional and behavioral evidence suggested early on that DA plays an important role in addiction, especially to psychostimulants (Dackis and Gold 1985; Wise 1984; Wise and Bozarth 1987). Subsequently, an impressive amount of research has confirmed that the DA system is fundamental in the development, maintenance, withdrawal and relapse phases of addiction (Koob and Volkow 2010; Robinson and Berridge 2008; Di Chiara and Bassareo 2007; Hyman et al. 2006; Hyman 2005; Everitt and Robbins 2005; Schultz 2011). In this article, we summarize several lines of evidences that demonstrate the role of DA in addiction and we briefly discuss how this knowledge has translated into clinical therapy and the lessons that could be learned from this field of research.

Addiction and the addiction cycle

Drug addiction is a chronic, relapsing psychiatric disorder that represents a major public health problem that impacts society on multiple levels, including health care, loss of productivity, police and crime/accident costs. The diagnostic and statistical manual of the American Psychiatry Association describes eleven criteria/symptoms that can be used to diagnose addiction in humans (DSM-5 2013). These criteria itemize the compulsive seeking and taking of the drug despite negative consequences, craving and a negative state that appears when the drug is withdrawn which are considered the key elements of addiction.

Addiction is characterized by phases of active, excessive consumption of the drug, phases of more controlled use, phases of abstinence and episodes of relapse (Koob and Volkow 2010; Volkow et al. 2004). Indeed, one of the criteria of addiction is that

individuals make unsuccessful attempts to reduce or quit drug consumption. Therefore, the pathology of addiction is often described as a cycle with three stages that are associated with different behavioral and neurobiological mechanisms: binge/intoxication, withdrawal/negative affect and preoccupation/anticipation (Koob and Volkow 2010, 2016; Koob and Le Moal 2001). The binge/intoxication stage is associated with positive reinforcement and stimulation of the reward system in which DA plays a major role during initial use of drugs and, as drug use becomes more habitual with stimulation of dorsal striatal regions (Koob and Volkow 2010, 2016). Conversely, the withdrawal stage is associated with negative affect, hypoactivity of the DA system and hyperactivation of the stress system, which drives negative reinforcement, i.e. drugs are taken not for their positive effects but to avoid negative emotional states. Finally, the preoccupation/anticipation stage is associated with craving for the drug, activation of cortical areas and release of DA in areas associated with emotions and memory such as the amygdala and the hippocampus (Koob and Volkow 2010, 2016).

The DA system

DA neurons, connectivity and activity

DA neurons are located in three main groups in the midbrain: A8 in the rutrorubral field, A9 in the substantia nigra pars compacta (SNc) and A10 in the ventral tegmental area (VTA). DA neurons from the VTA send projections to the nucleus accumbens (NAc) (meso-striatal system) and also provide inputs to other forebrain regions such as the prefrontal cortex (meso-cortical system) (Wise 2009; Haber and Knutson 2010; Haber et al. 1990). The SNc (nigrostriatal system) and the retrorubral area send projections to the dorsal striatum (DSt) (Wise 2009; Haber and Knutson

2010; Haber et al. 1990). Historically, the nigro-striatal pathway has been involved principally in the control of movement whereas the meso-cortico-striatal pathway has been involved in reward-learning and motivation. However, compelling evidence suggests that this clear-cut distinction is an oversimplification and that the DA system functions as a medial-to-lateral gradient of overlapping populations of DA neurons (Wise 2009).

DA neurons display multiple activity states: they can either be spontaneously active (firing) or silent (non-firing) (Figure 1, inset). The proportion of silent DA neurons appears to be maintained at a constant, hyperpolarized, inactive state by the ventral pallidum (VP) (Floresco et al. 2003). When DA neurons are spontaneously firing, they can fire with an irregular pattern (tonic activity) or displaying bursts of action potentials (phasic activity). Importantly, only spontaneously active DA neurons are able to fire in bursts (Lodge and Grace 2006) (Figure 1, inset). Thus, the proportion of neurons that fires spontaneously ("population activity") supplies the stable baseline level of extrasynaptic DA in postsynaptic structures and has been termed the "tonic" DA state (Grace 2000). Changes in firing from irregular tonic firing to burst phasic firing has been shown to be involved in reinforcement learning. Indeed, DA neurons display phasic burst first during the primary presentation with an unpredicted reward (Schultz 1998; Zweifel et al. 2011), but then, after conditioning with repeated stimulus-reward pairing, burst firing switches to the reward-predicting stimulus alone (positive prediction error) (Lammel et al. 2011; Zweifel et al. 2011; Schultz 1997). When the reward is not produced anymore after the stimulus, a pause in DA neurons firing occurs (negative prediction error). Therefore, firing of DA neurons appears to encode the signaling of reward prediction error, i.e. the difference between reward prediction and actual received reward (see following sections for more details).

Spontaneous activity of DA neurons is generated by intrinsic pace-making membrane properties of DA neurons themselves as demonstrated by the fact that tonic spiking activity is preserved in brain slice preparation, where the synaptic inputs have been severed (Deister et al. 2009; Shepard and Bunney 1988). In contrast, burst spiking is lost in such preparations, and is dependent on glutamate receptors activation, since local application of glutamate receptor antagonists disrupts this pattern, suggesting the necessity of synaptic inputs for the generation of this pattern of activity (Grace and Bunney 1984; Smith and Grace 1992). Indeed, burst firing is triggered by the transient interaction between ionotropic glutamate receptors and voltage-gated ionic channels (Grace and Bunney 1984; Hyland et al. 2002; Smith and Grace 1992).

Changes in DA activity state in the SNc and the VTA have consequences on the levels of DA in the NAc and the DSt respectively. Tonic DA activity is responsible for the basal levels (in the range of nM; (Sharp et al. 1986)) of extracellular DA in the striatum. Although this level of extracellular DA is relatively low, it is sufficient to induce a partial activation of DA D2 auto-receptors (Farnebo and Hamberger 1971), which results in suppression of most of the spike-dependent DA release. Conversely, phasic DA release corresponds to the rapid release of a significant amount (in the range of μM) of DA in the synaptic cleft (May et al. 1988) resulting from an activation of DA neurons in response to behaviorally salient stimulus, and leading to the activation of receptors on postsynaptic neurons (Grace 2000). DA is then rapidly removed from the synapse, by the DA transporter (DAT), and the signal is terminated. This massive but transient DA release can be measured in behaving animals by continuous amperometry (Benoit-Marand et al. 2011; Benoit-Marand et al. 2001; Benoit-Marand et al. 2000a) or fast scan cyclic voltammetry (Phillips et al.

2003a; Robinson et al. 2003) but not by techniques such as microdialysis or classical voltammetry (May et al. 1988).

VTA and SNc DA neurons receive different inhibitory and excitatory inputs that modulate their firing (Figure 1). The control of tonic firing of VTA neurons involves the bed nucleus of the stria terminalis (Georges and Aston-Jones 2001) and the ventral pallidum (Mahler et al. 2014; Grace et al. 2007), whereas the control of phasic firing in the VTA involves the pedoculopontine tegmentum (PPTg) and the laterodorsal tegmentum (Floresco et al. 2003; Lodge and Grace 2006). Burst firing in the SNc is driven by direct STN projection and the PPTg (Chergui et al. 1994; Futami et al. 1995; Hammond et al. 1978) and tonic firing in the SNc is regulated by the VP. Whereas projections from the VP to the DA and non-DA neurons in the VTA is monosynaptic (Hjelmstad et al. 2013), modulation of DA activity in the SNc by the VP is likely due to innervation from the substantia nigra pars reticulata (SNr). Indeed, inhibitory neurons from the SNr densely innervate the SNc (Grace and Bunney 1979; Tepper and Lee 2007; Tepper et al. 1995) and the pathway from the VP to the SNr is stronger than to the SNc because $GABA_A$ receptors are more sensitive in SNr GABAergic interneurons than SNc DA neurons (Celada et al. 1999; Grace and Bunney 1979; Tepper et al. 1995). Activity of DA neurons is also modulated by the lateral habenula (LHb) (Lecca et al. 2014). Thus, LHb stimulation has been shown to reduce firing of midbrain DA neurons (Ji and Shepard 2007; Christoph et al. 1986; Matsumoto and Hikosaka 2007). Since direct projection from the LHb to DA neurons is glutamatergic, this inhibition is suggested to be multisynaptic. A possible candidate is the rostromedial tegmental nucleus (RMTg, also called the tail of the VTA). Indeed, the RMTg receives strong innervation from the LHb (Kaufling et al. 2009) and sends strong GABAergic projections to DA neurons (Kaufling et al. 2009). It has been

shown that stimulation of the RMTg inhibits both the VTA and the SNc (Hong et al. 2011; Bourdy et al. 2014; Lecca et al. 2012), and RMTg inhibition increased DA neurons activity (Jalabert et al. 2011). Recently, Brown and collaborators have shown that RMTg neurons contribute directly to the LHb-induced inhibition of DA neurons activity (Brown et al. 2017). The RMTg receives afferents from a wide range of cerebral structures (for review see (Bourdy and Barrot 2012)) such as the cortex, the periaqueducal gray, the LDTg and PPTg, suggesting that the RMTg may integrate a variety of information that can modulate activity of both the VTA and SNc. It has been shown that a specific pathway that regulates the proportion of active DA neurons both in the SNc and the VTA is the ventral subiculum of the hippocampus (vSub)-NAc-VP-VTA/SNc pathway (Bortz and Grace 2018; Floresco et al. 2001c; Floresco et al. 2003). Two separate pathways from the NAc project to the VTA and the SNc: the NAc shell projects to the VTA and the NAc core projects to the SNc (Sesack and Grace 2010). Segregation is also likely to originate from the VP with the caudal VP projecting preferentially to the VTA and the rostral VP to the SNc (Mahler et al. 2014). Activity in the BLA decreases the population activity of DA neurons in the VTA, via a polysynaptic pathway, BLA-VP-VTA (Chang and Grace 2014) and this effect is under the control of the medial prefrontal cortex (mPFC) and, in particular, of the infralimbic cortex (Patton et al. 2013). There are major GABAergic feedback projections from the NAc/DSt and the VP into the VTA and the SNc (Kalivas 1993; Conrad and Pfaff 1976; Walaas and Fonnum 1980), forming parallel spiraling loops (Haber and Knutson 2010; Haber et al. 1990). Projections from the shell part of the NAc influence DA neurons in the VTA, which in turn projects to the core part of the NAc, which provides projections to the SNc, which sends its projection to the DSt (Haber and Knutson 2010; Haber et al. 1990). This is considered an anatomical base

for the hypothesis that transitions from goal-directed (voluntary) drug consumption to stimulus-response (habitual) drug use is dependent on this transition from medial/ventral neural circuits to more lateral/dorsal part of the VTA/SNc-NAc/DSt network (Everitt and Robbins 2005).

DA Receptor Subtypes and distribution

The diversity of DA receptors was revealed following the introduction of gene cloning procedures to the neurotransmitter receptor field (for a review see (Jaber et al., 1996)). DA receptors belong to the large family of G protein-coupled receptor (RCPG) and display considerable amino acid sequence conservation especially in their seven transmembrane domains. These receptors have been classified in 2 sub-families: D1 and D2. The D1/D2 classification concept developed in the late 1970s is still relevant even after the discovery of five distinct DA receptors. The D1 and D5 receptors are classified as "D1-like" because they share high sequence homology and stimulate the adenylate cyclase (AC) pathway and show classical pharmacological D1 responses (Jaber et al., 1996). The D2, D3, and D4 receptors are classified as "D2-like" and also share homologies. They mainly inhibit the AC pathway and show classical pharmacological D2 responses (Jaber et al., 1996). Members of the same family share common structural characteristics but have sequence variations that determine differences in their affinity for agonists and in the coupling to signal transduction pathways (Missale et al., 1998).

The D1 receptor (D1R) is the most widespread DA receptor and is expressed at a higher level than any other DA receptors (Dearry et al., 1990; Fremeau et al., 1991; Weiner et al., 1991). D1R mRNA is expressed in areas known to receive dopaminergic afferences such as the striatum, NAc and olfactory tubercle by

dopaminoceptive GABAergic neurons co-expressing dynorphin (Le Moine and Bloch, 1995; Le Moine et al., 1990) and to a lesser extent in the PFC. D1R mRNA is also found in the hypothalamus and thalamus. It is to note that in some brain areas D1R proteins are detected but not D1R mRNA suggesting that in these areas the D1 receptor is present in projections only.

The D2 receptor (D2R) gene contains exons and permits the generation of two splicing variants, named D2L and D2S (for long and short respectively) with the D2L mRNA being expressed at higher levels than the shorter variant (Jaber et al., 1996 for a review). It is mainly found in the olfactory tubercle and dorsal and ventral striatum where it is expressed by dopaminoceptive GABAergic neurons co-expressing enkephalins (Le Moine and Bloch, 1995; Le Moine et al., 1990). It is also found in the SNc and in the VTA, where it is expressed by dopaminergic neurons (Meador-Woodruff et al., 1992; Weiner et al., 1991). Thus, the D2R is expressed by both pre- and post-synaptic neurons.

The D3 receptor (D3R) has received considerable attention, mainly because it is specifically found in limbic areas such as the shell of the NAc, olfactory tubercle and islands of Calleja, and has low expression levels in the DSt (Bouthenet et al., 1991; Sokoloff et al., 1990).

Low levels of mRNA of the D4R are found in the basal ganglia whereas relatively higher levels in the frontal cortex, medulla, amygdala, hypothalamus and mesencephalon (O'Malley et al., 1992; Van Tol et al., 1991). However, the expression of the D4R remains weak when compared with expression of other DA receptors, including the D5R that is also notorious for its scarce expression. Indeed, the expression of D5R seems to be restricted to the hippocampus, the lateral mamillary nucleus and the parafascicular nucleus of the thalamus (Tiberi et al., 1991;

Meador-Woodruff et al., 1992) and the relative abundance of the DA receptors in the rat central nervous system would be D1› D2› D3› D5› D4 (Missale et al., 1998).

The co-localization of D1R and D2R within the same neuron has been the subject of debate for two decades in the literature. It seems now settled that the D1/D2 synergism is achieved not through co-localization of these specific receptors but through co-localization of receptors belonging the D1 and D2 families (Carter-Russel et al., 1995), i.e. the same neurons would express D1/D3/D4 or D2/D5 (Beaulieu and Gainetdinov, 2011).

DAT expression and function

The DAT belongs to the family of monoamine transporters that are Na+/Cl- dependent plasma membrane proteins present at nerve endings. These transporters control the levels of monoamines by rapidly re-uptaking the released neurotransmitter and thus limiting the temporal persistence and the spatial spread of monoamines (Jaber 2006). As such, monoamine transporters constitute a major element in determining the intensity and duration of monoamine transmission. DAT mRNA was found only in DA synthesizing neurons and the corresponding protein is localized within dopaminergic innervation of several regions including ventral mesencephalon, medial forebrain bundle and dorsal and ventral striatum (Ciliax et al. 1995). At the protein level, the DAT is present perisynaptically rather than within the synaptic cleft thus promoting volume and somewhat paracrine transmission, rather than the classic synaptic transmission that is contained spatially to the targeted post-synaptic dendrites (Garris et al. 1994). Interestingly, at the sub-cellular levels, the DAT was found to be present in intracellular compartments as well as at the plasma membrane of dendrites, cell body and axon terminals. This suggests that the DAT

may be actually releasing DA at the dendritic level close to DA cell bodies (Hersch et al. 1997) and that its addressing to the membrane is regulated by the DA tone. The DAT is at the center of a great deal of attention given its key role in regulating DA transmission but also because it is targeted by psychostimulants such as cocaine and amphetamine (Jaber 2006) .

Dopaminoceptive neurons and their glutamatergic afferents

The striatum not only receives dense DA projections from the VTA and the SNc but also glutamatergic inputs from multiple brain structures and each of these glutamatergic inputs plays a role in different aspects of addictive behaviors (Sesack and Grace 2010). The NAc receives glutamatergic inputs from the PFC (the infralimbic part projecting preferentially to the NAc core and the prelimbic part to the NAc shell) (Groenewegen et al. 1999), the hippocampus and the amygdala (Britt et al. 2012; MacAskill et al. 2012). The DSt receives glutamatergic inputs from sensori-motor cortex (McGeorge and Faull 1989), and from the thalamus (Wall et al. 2013).

In the striatum, DA released in the extracellular space activates DA receptors that are located on medium spiny neurons (MSNs). MSNs in the DSt can be divided into two types based on their projection structures and peptide/DA receptors expression. D1-dynorphin-substance P-expressing MSNs project to the SNr/GPi (direct pathway to basal ganglia output structures) and D2-enkephalin-expressing MSNs project to the GPe (indirect pathway) (for review, see (Gerfen and Surmeier 2011)). In the NAc, D2R-expressing MSNs project to the VP and D1R-expressing MSNs project mainly to the VTA and SNr, but some collaterals to the VP have also been described (Chang and Kitai 1985; Berridge and Robinson 1998; Tripathi et al. 2010). However, recent studies suggest that this dichotomy is not absolute and that the direct and indirect

pathways may contain both D1- and D2-expressing MSNs (Kupchik et al. 2015). In addition, in the NAc, a subpopulation of MSNs expressing both D1R and D2R has also been described (Bertran-Gonzalez et al. 2008). DA release in the striatum promotes opposite changes in synaptic plasticity at glutamatergic synapses depending on the neuronal type. In fact, long-term potentiation occurs onto D1-expressing MSNs and long-term depression onto D2-expressing MSNs (for review see (Gerfen and Surmeier 2011)). It has been hypothesized that an imbalance between D1R- and D2R-expressing MSNs may contribute to addiction (Volkow et al. 2013; Lobo and Nestler 2011), and that each type of MSNs may play a crucial role in the regulation of addiction-like behaviors (for review see (Yager et al. 2015)), likely due to drug use-induced persistent changes in the afferent control of MSNs.

DA and reinforcement/reward processes

The first indirect demonstration of a role of the DA system in reinforcement and reward circuit was the discovery by Olds and colleagues that brain stimulation of specific brain areas was rewarding (Olds and Milner 1954). Although at the time DA was not considered a neurotransmitter, these experiments clearly demonstrated that a specific circuit was involved in reinforcement.

Importantly, when it was established that DA is a neurotransmitter (Carlsson et al. 1957; Carlsson and Lindqvist 1963), it was rapidly demonstrated that it played a major role in rewarding processes as lesions of this system, and notably the nigro-striatal pathway, by 6-hydroxy-DA causes severe adipsia and aphagia in animal models (Ungerstedt 1971; Olds and Milner 1954). In addition, it was found that dopaminergic neurons were concentrated in areas that maintained self-stimulation, these experiments set up the background for experiments that demonstrated that self-stimulation reward depends on DA neurotransmission (Fouriezos et al. 1978).

In parallel to these experiments, Wise and colleagues started investigating the role of DA in the rewarding effects of more physiologically relevant stimuli such as food (Wise et al. 1978). They found that administration of the dopaminergic antagonist pimozide eliminated food reward. The effects of pimozide resembled those of extinction under condition of withdrawal of food reinforcement which lead Wise to suggest that pimozide prevented rats to experience the positive, rewarding consequence of consumption of food (Wise 1978). Several experiments have confirmed and extended this finding. Importantly, DA does not appear indispensable to drive feeding but it is necessary to motivate animals to exert an effort to obtain food (Salamone et al. 2007) and it appears to be sensitive to the novelty and the palatability of food (Di Chiara and Bassareo 2007). Finally, DA has been shown to be central for sexual reward and in particularly for its appetitive aspects (Damsma et al. 1992; Everitt 1990; Fibiger et al. 1992; Micevych and Meisel 2017).

A critical contribution to the understanding of the role of the DA system in reward processes comes from the work of Wolfram Schultz (Schultz 2016; Schultz et al. 1997). Using electrophysiological recording of dopaminergic region (notably the SN) in behaving non-human primates, they found that DA neurons respond to novel or better than expected rewards but that, upon repeated exposure and learning, they cease to respond to reward itself and instead they respond to stimuli that are predictive of reward and that are unexpected because their occurrence is not signaled (Schultz 2016; Schultz et al. 1997). Moreover, they found that DA neurons are inhibited when a reward is withdrawn or is worse than expected leading to the postulate that DA represent a learning signal for reward prediction errors (Schultz 2016; Schultz et al. 1997). Thus, increases in DA activity signal that something positive has occurred and that the current knowledge about rewards needs to be

updated to take into consideration the new knowledge and increase the probability of repeating the actions that produce the reward (Schultz 2016; Schultz et al. 1997). Conversely, decreases in DA activity signal that the expected reward is no longer available (ex. depletion of food resources) and current knowledge needs to be updated to take into consideration this novel information and decrease the probability of repeating the actions that fail to produce the reward and to increase the probability of implementing new actions (Schultz 2016; Schultz et al. 1997). Finally, DA activity does not change when reward is obtained as expected and knowledge of the state of the world does not need to be changed or updated (Schultz 2016; Schultz et al. 1997). Other theoretical framework to explain the role of DA in reward processes have been proposed such as incentive motivation (Berridge and Robinson 1998; Robinson and Berridge 1993), habit formation (Graybiel 1998; Everitt and Robbins 2005), aberrant learning and memory processes (Di Chiara et al. 1999; Hyman 2005; Hyman et al. 2006) and effort-related aspects of motivation (Salamone et al. 2007).

In humans, brain-imaging studies strongly suggest a role for the DA system in non-drug rewards. Indeed, the dopaminergic system is activated by food consumption and food-related stimuli, especially in people with obesity and eating disorders (Volkow et al. 2017). In addition, the dopaminergic system appears involved in sexual attraction and arousal as well as in romantic love (Fisher et al. 2005; Georgiadis et al. 2012; Ruesink and Georgiadis 2017). Interestingly, in humans, monetary reward is also associated with the activation of the DA system indicating that this system is able to respond to abstract and cultural constructions of reward (Koepp et al. 1998; Zald et al. 2004).

Drugs, DA and reinforcement

One of the key discoveries in determining the role of DA in brain reward processes and in addiction was the demonstration that all drugs, regardless of their specific mechanism of action, increase the extracellular levels of DA in the striatum. Using transversal microdialysis, Di Chiara and collaborators were able to demonstrate that cocaine, amphetamine, morphine, nicotine and alcohol (Imperato and Di Chiara 1986; Di Chiara and Imperato 1988) increase DA levels preferentially in the ventral striatum. A decade later, using vertical microdialysis probes that allow more precise sampling of different subregions of NAc it was found that acute, passive injections of drugs increase DA levels preferentially in the Shell rather than the Core region of the NAc (Pontieri et al. 1995; Pontieri et al. 1996; Tanda et al. 1997). Importantly animals self-administering cocaine according to a fixed-ratio (FR1) schedule control the frequency of cocaine injections in order to titrate DA levels in order to maintain them above a certain threshold (Wise et al. 1995b). These effects have been confirmed and extended to other drugs such as heroin, amphetamine, nicotine and cannabinoids (Lecca et al. 2006a; Lecca et al. 2006b; Lecca et al. 2007; Ranaldi et al. 1999; Wise et al. 1995a). Whereas DA in the NAc is indispensable for the initial effects of drugs and in the development of addiction when behavior is goal-directed, when behavior becomes more habitual, the dorsal striatal regions take over and play a major role (Zapata et al. 2010). In addition, the involvement of the NAc Core and the more dorsal region effects may be particularly critical for conditioned responses. For example, Ito et al (Ito et al. 2004; Ito et al. 2002; Ito et al. 2000) found that in rats self-administering cocaine according to a second order schedule that is maintained by drug cues, DA elevations induced by conditioned stimuli are specific for the NAc core and that drug seeking maintained by these cues was specific of the DSt. In

addition, blockade of DA receptors in the DSt prevents cocaine seeking (Belin and Everitt 2008; Vanderschuren et al. 2005) and relapse after prolonged abstinence (See et al. 2007).

Fast scan voltammetry can measure changes in DA levels with sub-second resolution and allows investigating changes in phasic DA releases (Robinson et al. 2003; Phillips et al. 2003a). This technique has also been instrumental to characterize the role of DA in addiction. In particular, it has been shown that injections of cocaine increase DA levels in the NAc in rats that actively self-administer this drug (Phillips et al. 2003b) but also that, in trained animal, increases of DA in the NAc levels occur before animals actually perform the action (lever press) that leads to cocaine delivery, further supporting the role of DA in driving drug-seeking behavior (Phillips et al. 2003b). Finally, it has been shown that phasic DA release decreases in the NAc, whereas it increases in the DSt after several weeks of access to short sessions of cocaine self-administration (Willuhn et al. 2012). However, under conditions of extended access to cocaine, the increase in the DSt appeared transient and after 3 weeks of cocaine escalation, no increase in DA levels was found following self-injections of cocaine (Willuhn et al. 2014). These results suggest that DA elevations occur in the initial stages of addiction but not after repeated excessive intake of drugs which may instead be associated with a sort of DA depletion as supported by the fact that L-dopa treatment restored DA signaling and blocked escalation of cocaine intake (Willuhn et al. 2014).

DA, drug withdrawal and negative affect

If drugs increase DA levels in the NAc when administered acutely or repeatedly, what happens when drug administration is discontinued? Homeostatic principles and the "opponent processes" theory (Solomon and Corbit 1974), predict that the body

should adapt to drug effects and produce adaptations that oppose and counteract these effects and therefore, DA levels in the NAc are expected to drop below basal levels, which would result in aversion and low mood. This concept and its role in addiction have been further developed by Koob and Le Moal in their allostatic theory of addiction (Koob and Le Moal 2001), which postulates that upon repeated cycles of intoxication and withdrawal the brain would be overwhelmed by drug-induced neuroadaptations and would not be able to restore normal activity levels of the reward system. Thus, individuals would find themselves locked in a low emotional state that would make them particularly vulnerable to the motivational effects of drug-related stimuli and stressors leading to accrued risks of relapse. Indeed, basal DA levels have been shown to be lower than normal during acute withdrawal from cocaine (Parsons et al. 1991; Weiss et al. 1992; Rossetti et al. 1992), morphine (Pothos et al. 1991; Rossetti et al. 1992; Crippens and Robinson 1994; Acquas et al. 1991), amphetamine (Rossetti et al. 1992; Crippens and Robinson 1994), alcohol (Rossetti et al. 1992; Weiss et al. 1996), nicotine (Hildebrand et al. 1998) and THC (Tanda et al. 1999). Conversely, activity of VTA DA neurons measured by in vivo electrophysiology has been shown to be altered with decreases found during withdrawal from alcohol (Diana et al. 1992b), morphine (Diana et al. 1995), THC (Diana et al. 1998) and increases found after cocaine (Ackerman and White 1990; Zhang et al. 1997), amphetamine (Zhang et al. 1997) and nicotine (Rasmussen and Czachura 1995).

In parallel, intracranial self-stimulation, a measure of the sensitivity of the reward system, has demonstrated that rats have deficits in self-stimulation reward after withdrawal from cocaine (Markou and Koob 1991), amphetamine (Paterson et al. 2000; Wise and Munn 1995), morphine (Schulteis et al. 1994), alcohol (Schulteis et

al. 1995) and nicotine (Epping-Jordan et al. 1998; Kenny and Markou 2001). Altogether, these findings suggest that withdrawal from drugs is associated with decrease activity of the dopaminergic system that may participate to a negative state and drive negative reinforcement. However, it should be noticed that most if not all of these effects have been found after hours or days of withdrawal and most of these dysregulations recover upon protracted abstinence (Koob 2006, 2008). Therefore, it is likely that neurotransmitter and neuroendocrine systems other than the DA systems are responsible for the persistent negative effect that may be associated with long-term abstinence (Koob 2006, 2008).

DA, craving and relapse

In addition to the phases of intoxication and withdrawal, DA plays a key role in craving and relapse to drugs. First of all, administration of low doses of the drug (i.e. drug priming), that induce DA elevations in the NAc, is a strong trigger of reinstatement (Shaham et al. 2003; Shalev et al. 2002) and these effects appear at least in part to be mediated by DA because DA receptor antagonists reduce drug seeking behavior (Shaham et al. 2003; Shalev et al. 2002; Andreoli et al. 2003; Higley et al. 2011; Norman et al. 1999; Liu and Weiss 2002). In addition, direct injections of DA agonists in the NAc trigger relapse to cocaine (Bachtell et al. 2005; Schmidt et al. 2006). Cue-induced and stress-induced reinstatement appears also to depend, at least in part, on DA neurotransmission (Mantsch et al. 2016; Crombag et al. 2008; Feltenstein and See 2008). However, when it comes to relapse, dopaminergic regions other than the NAc such as the DSt, the amygdala, the PFC and the hippocampus appear to play a major role in this phenomenon (Feltenstein and See 2008).

Addiction and DA brain imaging

In the last thirty years, brain-imaging techniques have provided considerable insights into the mechanisms underlying addiction (Volkow et al. 2009; Volkow et al. 2004). These non-invasive approaches have allowed for the first time to investigate the functional and structural alterations that are associated with addiction in humans allowing for the investigation of the changes that occur at different stages of addiction. Altogether, these studies have confirmed that drugs of abuse activate DA systems and that major modifications occur in the DA system in individuals suffering from addiction. For example, DA release induced by drugs has been estimated by PET brain imaging quantifying the displacement of DA receptor ligands (Volkow et al. 2009). It has been shown that acute administration of drugs of abuse such as amphetamine (Drevets et al. 2001; Leyton et al. 2002; Martinez et al. 2005), alcohol (Boileau et al. 2003; Urban et al. 2010), nicotine (Barrett et al. 2004; Brody et al. 2004), delta-9-tetrahydrocannabinol (Bossong et al. 2009) increase DA levels in the striatum, and increases in the NAc correlate with their euphoric effects (Volkow et al. 2009). However, addiction is generally associated with reduction in DA D2R availability in the striatum and these effects appear to persist even after several months of discontinuation of drug consumption (Volkow et al. 2009; Volkow et al. 2011). More importantly, release of DA by drugs in addicted individuals is blunted compared to drug-naïve controls which suggests that a sort of tolerance, rather than sensitization, to the reinforcing effects of drugs (Volkow et al. 2009; Volkow et al. 2011). Finally, similarly to what found in animals, drug cues increased DA release in the DSt but not the NAc (Volkow et al. 2006; Wong et al. 2006) and in the PFC (Milella et al. 2016) in people with cocaine use disorder but also in recreational cocaine users (Cox et al. 2017). Although functional magnetic resonance imaging

(fMRI) approaches cannot discriminate the effects of specific neurotransmitters, they also show that drugs and drug-related stimuli affect the activity of dopaminergic areas (Suckling and Nestor 2017; Zilverstand et al. 2018).

One of the most replicable alterations found in people suffering from addiction compared to controls, is that the levels of dopaminergic D2R in the striatum are decreased (Volkow et al. 2009; Volkow et al. 2004). Conversely, high levels of D2R reduce the positive effects of psychostimulants (Volkow et al. 2002; Volkow et al. 1999) and therefore, low levels of D2R could represent a risk factor for the development of addiction to psychostimulants as suggested by studies in animal models (Dalley et al. 2007; Morgan et al. 2002; Nader et al. 2006).

The development of brain imaging techniques for laboratory animals have further expanded the ability of these approaches and will allow to provide more mechanistic insights into addiction processes (Caprioli et al. 2013; Jonckers et al. 2015; Gould et al. 2014). Brain imaging studies in animals have mostly focused on cocaine, because this drug produces the most reliable self-administration behavior and allows producing addiction-like phenotypes in rats (Ahmed and Koob 1998; Deroche-Gamonet et al. 2004; Vanderschuren and Everitt 2004). In the last fifteen years, studies in non-human primates have allowed better understanding of addiction processes and its evolution over time (Gould et al. 2014). For example, they have demonstrated that over the course of chronic self-administration the reduction in brain metabolic activity induced by cocaine shifts from the ventral to the DSt (Porrino et al. 2004). In rats with a history of escalation of cocaine self-administration reduction in brain metabolic activity of the ventral striatum has been reported after short periods of withdrawal (Calipari et al. 2013; Gozzi et al. 2011; Nicolas et al.

2017). However, after longer periods of abstinence, the reduction in brain metabolic activity was found in dorsal striatal regions (Nicolas et al. 2017).

Electrophysiological effects of drugs on the DA system

Effects of acute administration of drugs on the activity of DA neurons

The population activity (i.e. the proportion of DA neurons that are active at a given time), the firing rate and the firing pattern of SNc and VTA dopaminergic neurons are major determinants of the levels of DA released from terminals, to their targets, the DSt and the NAc respectively (Hedreen and DeLong 1991; Lynd-Balta and Haber 1994; Szabo 1979). We will describe findings that mostly refer to VTA DA neurons, which have been more widely studied in the field of addiction than SNc DA neurons.

Psychostimulants (such as cocaine and amphetamine) decrease the firing and bursting rate of DA neurons recorded from the VTA and the SNc. Cocaine blocks the reuptake of DA, and amphetamine inverts DA transport in the presynaptic neurons thereby increasing DA release, ultimately inducing the activation of negative feedback mechanism from forebrain structures. Psychostimulants also increase DA levels in the VTA, which can activate D2R present on the soma and dendrites of DA neurons, as well as D2-autoreceptors located on terminals, and further inhibits dopaminergic activity (French 1997; Lodge and Grace 2005; Belujon et al. 2016; Bunney et al. 1973; Einhorn et al. 1988; Groves et al. 1975). Notwithstanding this reduction in VTA activity, the net effect of psychostimulant administration is an increase in DA levels in the NAc and the VTA, which suggests that the effect of cocaine on DAT is sufficient to elevate extracellular DA levels (Chen and Reith 1994). Acute injections of amphetamine have also been shown to decrease burst firing and population activity of DA neurons in the VTA (Belujon et al. 2016; Lodge

and Grace 2008). Most of these changes after acute drug exposure are transient, but are likely to play a role in the development of addictive behavior (for review, see (White and Wolf 1991)).

For other substances of abuse (such as ethanol, morphine, nicotine and cannabinoids), acute drug exposure increases the spontaneous activity, in terms of firing rate and bursting activity of VTA and SNc DA neurons (Diana 1998; Gessa et al. 1985; Grenhoff et al. 1986; French 1997; Budygin et al. 2004). Opiates act on mu-opioid receptors and disinhibit DA neurons in the VTA through indirect inhibition of GABAergic inputs (Johnson and North 1992; Luscher and Ungless 2006). Systemic and intra-VTA infusion of morphine has also been shown to increase the firing rate and bursting activity of DA VTA (Jalabert et al. 2011). Although the mechanism of action of alcohol has not yet been fully understood, it is established that glutamate and GABA receptors play an important role in alcohol reinforcement (Luscher and Ungless 2006). Intra-VTA administration of ethanol produces an increase of DA levels in the NAc, suggesting that one the main sites for ethanol reinforcement is the VTA and the consequent activation of DA neurons (Beveridge et al. 2009). Consistent with this idea, it has been shown that ethanol is voluntarily self-administered in the VTA (McBride et al. 1999). *In vivo* (Foddai et al. 2004; Mereu and Gessa 1984) and *in vitro* (Brodie et al. 1999) studies have shown that ethanol stimulates the firing activity of both VTA and SNc DA neurons, mediated via the inhibition of potassium M-current (Koyama et al. 2007). This increase in spontaneous activity of DA neurons is associated with an increase in DA release in the NAc and DSt (Fadda et al. 2005; Zhang et al. 2009).

Acute administration of psychostimulants has been shown to suppress NAc neurons firing by multiple mechanisms (for review see (White and Kalivas 1998)). In fact, using *in vivo* preparations, it has been shown that psychostimulants elicit either an inhibitory or excitatory response in NAc MSNs, depending on the depolarized (up) or hyperpolarized (down) state, where inputs from the hippocampus can gate cortical inputs by driving NAc neurons in the up states (O'Donnell and Grace 1995). Indeed, suppression of hippocampal afferents results in the elimination of the “up” state of NAc MSNs, and the failure to evoke spike firing after activation of prefrontal inputs to the NAc (O'Donnell and Grace 1995). Acute injections of methamphetamine induce a loss of the up and down states fluctuations in the NAc, with a resting membrane potential more depolarized than baseline (Brady et al. 2005). It should be noted that the information flow from principal glutamatergic inputs to NAc MSNs arising from the prefrontal cortex, hippocampus and amygdala (Groenewegen et al. 1999) depends on DA (Floresco et al. 2001a; Belujon and Grace 2014; Floresco et al. 2001b). Indeed, changes in DA release in the NAc have been shown to have an effect on DA inputs as well as glutamatergic inputs onto MSNs.

Other drugs, such as ethanol, nicotine or opioids affect MSNs. For example, acute ethanol has been shown to inhibit MSNs in the DSt via changes in cholinergic tone (Blomeley et al. 2011). Indeed, ethanol inhibits cholinergic and low-threshold interneurons, while it excites fast-spiking ones. The reduction of acetylcholine induces a large hyperpolarization of MSNs, which leads to downregulation of GABA and glutamate receptors in MSNs (Blomeley et al. 2011). Conversely, acute opioids in the DSt appear to inhibit cortico-striatal synapses at the presynaptic level. Indeed, it has been shown that *in vitro* opioids agonists selective for mu- and delta- receptors presynaptically inhibit excitatory synaptic potentials in MSNs, whereas only delta-

selective agonists decrease inhibitory synaptic potentials (Jiang and North 1992). Acute opioids have also been shown to produce long-term depression (LTD) in the DSt. Thus, *in vitro*, application of an opioid receptor agonist induced a long-lasting reduction of electrically evoked EPSCs amplitude in the DSt (Atwood et al. 2014). In addition, a robust inhibition of glutamatergic synaptic inputs to MSNs neurons by application of a mu-agonist has been reported also *in vitro* in the NAc (Hoffman and Lupica 2001). The same study reported no effect of mu-agonists of GABAergic synaptic responses in the NAc. On the other hand, glutamatergic inputs are only marginally inhibited by cannabinoids, whereas GABAergic inputs are consistently inhibited (Hoffman and Lupica 2001). It has been suggested that this presynaptic inhibition is due to activation of CB1 receptors located on the terminals of a small population of interneurons in the NAc, playing a critical role in feed-forward inhibition of MSNs outputs (Hoffman and Lupica 2001). Finally, acute nicotine has been shown to facilitate endocannabinoid (eCB)-long-term depression in the DSt (Adermark et al. 2018). This facilitation is occluded by a D2 agonist, as well as a muscarinic acetylcholine antagonist, suggesting that nicotine affects DA and cholinergic neurotransmission in the DSt (Adermark et al. 2018). Indeed, it has been shown behaviorally that nicotine releases endogenous cannabinoid that can produce THC-like discriminative effects (Solinas et al. 2007) and that this effect resembles that of DA agonists (Solinas et al. 2010a), suggesting that the three systems convey converging information (for review see (Gamaleddin et al. 2015)).

Therefore, the actions of different drugs of abuse on synaptic processes in the striatum participate in the modulation of activity of MSNs and likely contribute to addictive properties of these drugs.

Effects of chronic administration of drugs on the neuronal activity of DA neurons

Whereas acute administration of psychostimulants induces a DA-mediated feedback inhibition of DA neurons activity, after a chronic regimen, and eventually the discontinuation of the drug administration, different and sometimes opposite effects can be found. For example, seven days after withdrawal from chronic cocaine, VTA DA neurons population activity is increased (Lee et al. 1999; Gao et al. 1998). This effect is reversed by blockade and desensitization of D2R, suggesting changes in the function of D2R involved in feedback inhibition in the VTA-NAc pathway (Lee et al. 1999; Gao et al. 1998). Wolf and collaborators in 1993 have also shown in chronically amphetamine-treated rats that VTA DA neurons were sub-sensitive to the D2 agonist quinpirole after short-term withdrawal but not after longer period of withdrawal (Wolf et al. 1993). Repeated cocaine administration induced an increase in the firing rate and the number of spontaneously active DA neurons in the VTA (Henry et al. 1989).

Chronic treatment with cannabinoids has been shown to not alter spontaneous activity of VTA and SNc DA neurons *in vivo* 24h after the last injection of cannabinoid (Wu and French 2000). In contrast, chronic morphine (Diana et al. 1995) and nicotine (Rasmussen and Czachura 1995) induce a significant decrease in the firing rate and the bursting rate of VTA neurons and chronic nicotine had no effect on SNc DA neurons (Rasmussen and Czachura 1995). *In vivo*, chronic ethanol has been shown to induce an increased in the spontaneous activity of VTA DA neurons (Diana et al. 1992a) whereas *in vitro* studies found no differences between ethanol and naïve-treated rats (Brodie 2002). However, in this study, a sensitization to ethanol

excitation of DA VTA neurons has been observed, suggesting that alcohol induced adaptations of DA neurons. Indeed, DA neurons undergo adaptive changes that might be unmasked during withdrawal from drugs of abuse (Brodie 2002).

Effects of chronic administration of drugs on the activity of NAc and DSt neurons

Several studies have suggested that the NAc and the DSt are subjected to neurobiological changes as drug use develops from acute to chronic, both in animal models (Macey et al. 2004; Nader et al. 2002) and in humans (Hanlon et al. 2009). For example, during chronic self-administration of cocaine, MSNs recorded from the NAc core show a strong phasic inhibition during the beginning of the operant training, that become blunted across sessions (Coffey et al. 2015). However, the activity of MSNs recorded from the NAc shell, as well as MSNs from the DSt remained stable throughout several sessions of self-administration (Coffey et al. 2015). These results suggest that different parts of the striatum have some distinct functional neuroadaptations during chronic drug use that may participate differently in pathological processing of drug-related information.

Chronic methamphetamine reduces the up-state duration in NAc MSNs implying that MSNs will be less responsive to afferent inputs, the balance among excitatory inputs is disrupted, suggesting an inappropriate processing of irrelevant information (Brady et al. 2005). Indeed, DA in the NAc is thought to play a role in mediating the selection of appropriate input processing by NAc MSNs (O'Donnell 2003; Floresco et al. 2003). Therefore, disruption in the gating function in the NAc after chronic methamphetamine implies a disruption in the filtering of irrelevant information (Brady et al. 2005), which could lead to an increased level of salience for drug-associated

cues. After protracted periods of withdrawal from chronic amphetamine (>20 days), alterations in the cortico-accumbens circuit have also been observed, i.e. increased bistable membrane activity, and increased intercellular coupling in the PFC and NAc (Onn and Grace 2000). Interestingly, these changes were not observed during the chronic administration, suggesting that withdrawal from amphetamine unmasked alterations in the cortico-accumbens circuit (Onn and Grace 2000).

Addiction, DA and Synaptic plasticity

Addiction has long been associated with pathological neuroplasticity in the mesolimbic system, as reviewed thoroughly previously (Luscher and Malenka 2011; Gipson et al. 2014; Jones and Bonci 2005; Kauer and Malenka 2007; Hyman et al. 2006; Nestler 2001; Wolf and Ferrario 2010; Russo et al. 2010). Here we review the main findings in different regions of the DA system.

VTA

Synaptic plasticity in the VTA is modulated by different drugs of abuse and is thought to contribute to different and specific aspects of addiction. Both excitatory and inhibitory inputs onto DA neurons in the VTA undergo long-term changes after acute and/or chronic exposure to drugs (Luscher and Malenka 2011). Many studies have demonstrated an enhancement of glutamatergic synaptic transmission in the VTA induced by acute (Ungless et al. 2001; Wanat and Bonci 2008) and chronic (Borgland et al. 2004) cocaine. A seminal study, published in 2001 has shown that an acute injection of cocaine was sufficient to induce long-term potentiation of AMPA-mediated currents at excitatory synapses onto DA VTA neurons, that persists until 5 days after the injection; an occluded induced-LTP as well as an enhanced LTD has also been described (Borgland et al. 2004) suggesting that this potentiation might be

involved in the early stages of the development of addiction. For both acute and chronic studies, this potentiation was transient and lasted less than 10 days (Ungless et al. 2001; Wanat and Bonci 2008; Borgland et al. 2004), and might contribute to the increase in DA neurons firing observed after a 24h withdrawal from chronic cocaine (Henry et al. 1989). A single exposure to ethanol has also been shown to induce synaptic plasticity changes. Thus, acute ethanol abolishes completely the long-term depression induced by high frequency stimulation (HFS) of GABAergic inputs to the VTA (Guan and Ye 2010), and it reduces the expression of LTP at glutamatergic synapses onto VTA neurons (Wanat et al. 2009). Another study has shown that self-administration of cocaine, but not passive cocaine infusions, produced persistent potentiation of VTA excitatory synapses, still present after 3 months of abstinence and resistant to behavioral extinction, whereas sucrose or food self-administration induced only a transient potentiation of VTA glutamatergic signaling (Chen et al. 2008). These data suggest that the pharmacological effect of cocaine itself is not sufficient to potentiate VTA glutamatergic signaling, and that the drug-context pairing is necessary to induce persistent changes in synaptic plasticity. Similarly, amphetamine enhances AMPA/NMDA ratio at excitatory synapses onto VTA DA neurons (Faleiro et al. 2004), although the specific mechanism seems different from cocaine (Wolf and Tseng 2012).

Chronic ethanol induced an increase in AMPA receptor functions in the VTA (Stuber et al. 2008), which is similar to LTP-processes (Bonci and Malenka 1999), and may facilitate the drive to consume ethanol. Acute morphine induced a loss of potentiation at GABAergic synapses onto VTA DA neurons and enhanced glutamatergic synapses 24h after exposure, as described with nicotine. Thus, all addictive drugs tested *in vitro* induce a potentiation of AMPA/NMDA ratio in VTA DA neurons after *in*

vivo administration of a single dose (Borgland et al. 2004). Moreover, addictive drugs (such as cocaine, nicotine and morphine) have been shown to induce the insertion of GluA2-lacking calcium-permeable AMPAR (CP-AMPA) into the synapses in the VTA (Argilli et al. 2008; Bellone and Luscher 2006; Brown et al. 2010)

SNc

A single exposure to drugs and in particular psychostimulants, also alter the activity of SNc DA neurons and play a role in the increased expression of behavior mediated by DA release in the DSt (Zahniser et al. 1998; Wolf 1998). A recent study, using optogenetics, has highlighted changes in specific glutamatergic afferents onto SNc neurons following a single cocaine exposure (Beaudoin et al. 2018). Whereas previous studies showed that a single exposure to cocaine increases EPSCs in the VTA but failed to find an effect in the SNc (Ungless et al. 2001; Lammel et al. 2011), this could be due to the use of non-specific electrical stimulation of SNc DA neurons excitatory inputs. Thus, cocaine-induced plasticity appears to be dependent on the types of afferents involved, specifically the STN-SNc and PPTg-SNc (Beaudoin et al. 2018). DA neurons from the SNc can selectively modulate the information processed by different input nuclei. For example, the AMPA/NMDA ratio is decreased at the PPTg-inputs to SNc, whereas it is unchanged in the STN-inputs to SNc (Beaudoin et al. 2018).

NAc

Several studies have found that cocaine exposure, whether acute or chronic, alters the capacity of NAc glutamatergic synapses to undergo synaptic plasticity (Fourgeaud et al. 2004; Goto and Grace 2005; Yao et al. 2004; Martin et al. 2006).

Synaptic plasticity is often studied by examining excitatory synaptic transmission using the ratio AMPA/NMDA-mediated excitatory postsynaptic currents (EPSCs). Unlike in the VTA, a single cocaine injection is not sufficient to cause by itself changes in the synaptic strength in the NAc, when measured 24h later (Kourrich et al. 2007; Thomas et al. 2001), but it can induce changes in the induction of low-frequency induced-LTD in indirect pathway MSNs (Grueter et al. 2010). However, chronic cocaine reduces AMPA receptors in NAc shell, not core, MSNs, and decreases synaptic strength at excitatory cortical synapses (Kourrich et al. 2007; Thomas et al. 2001), which is similar to what has been described after chronic amphetamine, i.e. a decrease in AMPA receptor levels in the NAc (Lu and Wolf 1999). These synaptic adaptations in the NAc have been shown to follow and to depend on changes in the synaptic function described in the VTA, i.e. potentiation of excitatory inputs (Mameli et al. 2009). Moreover, some studies have shown an increase in AMPA receptors EPSC after cocaine treatment followed by protracted abstinence (14 days), suggesting that cocaine produces a potentiation of excitatory inputs that develops or is unmasked during withdrawal (Kourrich et al. 2007; Ortinski et al. 2012; Boudreau and Wolf 2005).

In the last 15 years, particular attention has been given to changes in plasticity in the NAc which are associated with the phenomenon of incubation of cocaine craving (Grimm et al. 2001). A critical mechanism, thoroughly reviewed by Wolf and collaborators (Wolf 2016; Dong et al. 2017) is the synaptic accumulation of CP-AMPA at excitatory synapses on MSNs in the NAc. Indeed, whereas GluA2-containing calcium-impermeable AMPA (CI-AMPA) receptors are responsible for the majority of excitatory synaptic transmission in drug-naïve rats or during short withdrawal from chronic cocaine, during protracted abstinence, the contribution of

CP-AMPA receptors increases, which leads to an increased responsiveness of MSNs to glutamate (Purgianto et al. 2013). Other studies highlighted the role of silent synapses in the incubation of craving (Lee et al. 2013; Ma et al. 2014). First, it has been shown that silent synapses (expressing stable NMDA receptors but absent or labile AMPA receptors) become unsilenced as the withdrawal period progresses, a process that involves CP-AMPA receptors. Recruitment of CP-AMPA receptors has been shown in amygdala-NAc synapses (Lee et al. 2013) as well as in infralimbic PFC-NAc synapses (Ma et al. 2014). Interestingly, optogenetic stimulation induces downregulation of CP-AMPA at these two different synapses but reduces incubation of craving only in amygdala-NAc synapses, whereas downregulation of CP-AMPA receptors in infralimbic PFC-NAc synapses increases incubation of craving (Lee et al. 2013; Ma et al. 2014), suggesting that reorganization of specific circuits is critical for relapse.

Dorsal striatum

Whereas drug-induced deregulation of synaptic plasticity has been well studied in the NAc, limited evidence exists regarding drug-induced synaptic plasticity in DSt. A study in primates chronically exposed to ethanol has shown that MSNs of the putamen exhibited enhanced glutamatergic transmission as well as an increased intrinsic excitability (Cuzon Carlson et al. 2011).

Chronic nicotine induced a change in the regulation of cortico-striatal synaptic plasticity, in particular in the indirect pathway (D2 MSNs). Indeed, whereas in control animals, application of HFS normally induced an LTD, in animals chronically treated with nicotine, HFS induced an LTP, therefore inverting the direction of plasticity (Xia et al. 2017), an effect likely mediated by disruption of DA signaling (Koranda et al.

2014). Metabotropic glutamate receptors of subtype 5 (mGluR5) in the striatum are necessary for the induction of LTD (Sung et al. 2001) and mGluR5 function appears to be altered following abstinence from cocaine self-administration (Knackstedt et al. 2014). In particular, mGluR5-dependent LTD in DSt slices could not be induced following 3 weeks of abstinence from self-administration which was restored by the application of a positive allosteric modulator of mGluR5 (Knackstedt et al. 2014). This led the authors to suggest that pharmacological enhancement of GluR5 function could be a novel target to restore normal plasticity in the DSt and reduce the risk of relapse.

Addiction and DA structural plasticity

Drugs of abuse produce structural changes within the brain, and in particular within the mesolimbic dopaminergic system. The term “structural plasticity” refers to the reorganization of synaptic connections in brain circuits (Robinson and Kolb 2004). The interaction between neurons can be physically increased by the formation of new synaptic “boutons” and/or of new dendritic spines or reduced by their elimination. Dendritic spines are highly dynamic and the morphology of dendritic arborization can evolve rapidly to modulate the synaptic contacts between neurons (Berry and Nedivi 2017). The first demonstration that drugs of abuse can increase the dendritic arborization of neurons was provided by Kunz and collaborators that showed an increased spine density in the hippocampus in response to alcohol (Riley and Walker 1978; Kunz et al. 1976). Later on, Kolb and Robinson showed that chronic administrations of cocaine and amphetamine produce an increase in spine density on MSNs in the NAc shell and core (Lee et al. 2006; Maze et al. 2010; Norrholm et al. 2003; Robinson et al. 2001; Robinson and Kolb 1997, 1999). Chronic cocaine administration also increased spine density in the PFC, a brain area also targeted by

DA neurons from the VTA (Robinson and Kolb 2004). Similar increases have also been described in response to nicotine (Brown and Kolb 2001), MDMA (Ball et al. 2009), methamphetamine (Jedynak et al. 2007) and THC (Kolb et al. 2018). On the contrary, chronic alcohol (Zhou et al. 2007) and morphine (Robinson and Kolb 1999), decrease the spine density in the NAc. These structural changes, initially described in response to repeated administration of drugs, have also been found after a single administration of cocaine (Dos Santos et al. 2017). Interestingly, abstinence from drug has also been shown to produce alterations in dendritic spines that may participate in the withdrawal symptoms and the negative affect state that characterize this phase of addiction (Spiga et al. 2014a). Thus, acute or chronic administration of drugs produce long-lasting structural changes in the brain and particularly in the connectivity between DA neurons and striatal neurons.

Striatal structural changes in MSNs induced by drugs are mediated, at least in part, by DA. Indeed, structural changes found in culture of MSNs or *in vivo* after administration of cocaine depend on increases in the extracellular DA concentration (Fasano et al. 2013; Martin et al. 2011) and the stimulation of DA receptors (Dos Santos et al. 2017; Ren et al. 2010; Zhang et al. 2012). The increase in the density of dendritic spines observed after cocaine exposure was initially reported in both D1R- and D2R-expressing DA neurons but appears to be more durable in D1R-expressing neurons (Lee et al. 2006). More recent reports also indicate that this increase mainly occurs in D1R-expressing MSNs (Gipson et al. 2014; Gipson and Olive 2017; Kim et al. 2011; Russo et al. 2010). Interestingly, it was recently shown that this increased number of spines of MSNs is not associated with an increased number of

glutamatergic boutons (Heck et al. 2015), but instead with an increased number of dopaminergic boutons in the NAc Core (Dos Santos et al. 2018).

These drug-induced neuroplastic structural adaptations might modify communications within the dopaminergic system and could be part of the "drug memory" responsible for the high risk of relapse to drug addiction. In fact, NAc MSNs play a central role in the integration of cortical and mesencephalic afferents in distal spines of dendrites. This striatal "microcircuit" is thought to allow DA to influence cortical glutamatergic axons (Spiga et al. 2014b). Consequently, changes in dendritic spines by drugs might participate in synaptic plasticity described in response to drugs and in the behavioral consequences of their administration. For example, blockade of the Mitogen Activated Protein kinase ERK pathway prevents formation of new synapses in response to cocaine *in vitro* and *in vivo* (Dos Santos et al. 2017) as well as the behavioral effects of cocaine (Valjent et al. 2010; Valjent et al. 2006). Therefore, the long-lasting structural remodeling induced by acute or repeated drugs might play a role in the development and persistence of drug addiction (Brown et al. 2011; Robinson and Kolb 2004).

Drugs and transcriptional plasticity in DA regions

The consequence of drug-induced increases in DA transmission in the NAc is an over-stimulation of post-synaptic MSNs by activation of dopaminergic receptors, mainly D1R and D2R, that modulate the cyclic AMP pathway (Jaber et al. 1996). In addition, dopaminergic receptors interact with pathways activated by glutamatergic transmission and particularly the pathway involving ERK (Girault et al. 2007; Valjent et al. 2000). These rapid and transient effects of cocaine play a major role in triggering long-term molecular adaptations within dopaminoceptive regions, and particularly in the ventral and dorsal striatum and PFC (Pierce and Kalivas 1997;

Pierce and Wolf 2013; Wolf 2010, 2016). In fact, drugs activate constitutive transcription factors, such as the cAMP responsive element binding (CREB), that produce persistent changes in neuronal functioning that are believed to be central for addiction (Briand and Blendy 2010; Carlezon et al. 2005; Nestler 2004). Interestingly, CREB activation has also been shown to participate to the formation of new dendritic spines (Brown et al. 2011). CREB targets several genes including those of the immediate early gene *fos* or *egr* family (Beckmann and Wilce 1997; Janknecht 1995), which encode inducible transcription factors, and as a consequence, produce durable protein expression changes. Acute administration of cocaine (Hope et al. 1992; Thiriet et al. 2001a), amphetamines (Moratalla et al. 1992; Thiriet et al. 2001b; Graybiel et al. 1990), nicotine (Kiba and Jayaraman 1994; Ren and Sagar 1992), opiates (Bontempi and Sharp 1997; Garcia et al. 1995; Liu et al. 1994), THC (Mailleux et al. 1994; Valjent et al. 2002) and alcohol at high doses (Thiriet et al. 2000) have been shown to trigger the expression of immediate early genes of the *fos* and *egr* families in the striatum and the PFC. Usually, the expression of transcription factors of the Fos protein family is rather transient and tolerance to this response has been described with chronic passive administration of cocaine (Alibhai et al. 2007; Hope et al. 1992). In contrast, chronic administration of drugs was shown to produce an accumulation of Delta-Fos B (DFosB) in several brain regions, involved in addiction, namely the NAc, the DSt, the PFC, the hippocampus and the amygdala (Hope et al. 1994; McClung et al. 2004; Nestler et al. 2001; Perrotti et al. 2008) DFosB is a truncated form of the FosB protein, and present a much higher stability than FosB (Chen et al. 1997). Because of this stability, DFosB accumulates in neurons even after drug intake discontinuation and it is thought to be one of the main molecular adaptations involved in the long-term effects of drugs and to participate in

the switch to addiction (Nestler 2001). As for structural plasticity changes, accumulation of DFosB following drug administration takes place mostly in the D1R-expressing MSNs (Colby et al. 2003; Kelz et al. 1999; Lafragette et al. 2017; Lobo et al. 2010). By acting on this panoply of transcription factors in brain regions targeted by the dopaminergic system, drugs of abuse produce molecular adaptations and change the expression of proteins of different classes, which will have consequences both structurally and functionally within this system.

Drugs and molecular adaptations within the DA system

There are many discrepancies concerning the effects of drugs of abuse on elements of the DA system (i.e. the DA transporters and receptors) probably because of the different protocols used for drug administration (acute *vs* chronic, short *vs* long, passive *vs* active, etc) and the time from the last administration (from a few hours to several days) (McGinty et al. 2008). For example, some studies found a decrease in the levels of mRNA of the DAT immediately after chronic exposure to cocaine in the SN and VTA (Letchworth et al. 1997; Xia et al. 1992) whereas other studies found no effect (Arroyo et al. 2000; Maggos et al. 1997). In contrast, after 10 days withdrawal of cocaine self-administration an increase in DAT levels was found in the VTA but not in the SN (Arroyo et al. 2000), but not after passive administration (Cerruti et al. 1994). In rats, an increase in DAT binding in the NAc was found 1h after the last administration of moderate doses of cocaine (Letchworth et al. 1997) and a decrease in DAT binding after 10 days of withdrawal (Cerruti et al. 1994). However, withdrawal from cocaine self-administration results in an increase in DAT binding in rats with short access to cocaine, whereas rats that have extended access to cocaine and show escalation of self-administration do not show any difference compared to controls (Ben-Shahar et al. 2006). Finally, Letchworth et al. found a decrease in the

levels of DAT in the DSt after initial stages of self-administration but then, as self-administration becomes more chronic, they found an increase in the NAc (Letchworth et al. 2001). Importantly, these levels remained elevated after 30 days of withdrawal and returned to control levels only after 90 days of abstinence (Beveridge et al. 2009). The effects of other drugs of abuse on DAT have been less studied but no change in DAT levels was found after methamphetamine (Shepard et al. 2006) and heroin (Pattison et al. 2014) self-administration whereas alcohol increases DAT levels in the NAc of Wistar–Kyoto rats (Jiao et al. 2006).

Concerning DA receptors, controversial results have also been obtained. Increases, decreases, or no changes in the levels of D1R and D2R have been reported depending on the protocol of administration, time from the last injection and the technique of detection used (binding *vs* mRNA levels) for cocaine (Unterwald et al. 1994; Kunko et al. 1998; Sousa et al. 1999; Laurier et al. 1994; Ben-Shahar et al. 2007), amphetamines (Stefanski et al. 1999; Stefanski et al. 2002), alcohol (Cowen and Lawrence 2001; Hamdi and Prasad 1993; Tajuddin and Druse 1996; Eravci et al. 1997) and morphine (Georges et al. 1999). Interestingly, changes in receptor-mediated signal transduction have been shown for cocaine and morphine at the D1R leading to increased stimulation of the cAMP/ cAMP-dependent protein kinase (PKA) pathway (Hummel and Unterwald 2002; Terwilliger et al. 1991; Unterwald et al. 1996). In addition, changes at the levels of G-protein, especially to lower levels of the Gαi protein, which has an inhibitory function on the cAMP/PKA pathway have also been observed after drug administration (Nestler 1996; Terwilliger et al. 1991).

Although these preclinical results highlight the complexity of the neuroadaptations induced by drugs on the dopaminergic systems, as detailed earlier, studies in humans using PET tracers for DA receptors have been much more consistent and

have shown that people suffering from addiction to different drugs have lower levels of D2R in the striatum (Volkow et al. 2009; Volkow et al. 1993). In addition, methamphetamine users show also reduced striatal levels of the DAT (Chang et al. 2007).

Genetically modified animals, DA and Addiction

In the last 25 years, development of mice with mutations targeting members of the DA system has provided a wealth of information regarding the mechanisms of action of drugs of abuse and the synaptic plasticity occurring following these manipulations. Mice with a specific mutation of DAT or one of the five DA receptors have also been used to determine the specificity of action of a given drug, mainly, but not only, psychostimulants. Most studies have used classic knock-out (KO) procedures and some have implemented knock-down, knock-in or overexpression of some of these elements of the DA system. The genetic manipulation that has probably most impacted this research field may well be the knocking down of the DAT and its consequences on drug action, use, abuse and addiction. In this section, we will summarize main findings following various forms of genetic manipulation of elements of the DA system and further discuss their relevance in the behavioral and cellular responses to various drugs of abuse.

Genetic manipulations of the DAT and responses to drugs of abuse

a. DAT knock-out animals

DAT-KO mice have been generated over 20 years ago and were the first KO of any neurotransmitter transporter (Gainetdinov 2008; Giros et al. 1996; Jaber et al. 1997). Since that time, these mice have provided a wealth of information as to the action of

drugs of abuse on the DA system. Using these mice, it was shown that the DAT is involved in the lifetime control of extracellular DA (Benoit-Marand et al. 2000b; Giros et al. 1996; Jones et al. 1998), maintenance of pre-synaptic DA functions such as autoreceptor regulation (Benoit-Marand et al. 2000b; Jones et al. 1999), DA synthesis (Jaber et al. 1999) and storage mechanisms (Jones et al. 1998), as well as postsynaptic regulation such as receptor endocytosis (Dumartin et al., 2000) and gene expression (Fauchey et al. 2000a; Fauchey et al. 2000b).

DAT-/- mice present a hyperactive DA phenotype that is reflected behaviorally by several abnormalities due to a dysfunction within (i) the dopaminergic mesolimbic system (locomotor hyperactivity, lack of habituation to novelty and increased response to environmental stimuli) (Spielewoy et al. 2000), (ii) the dopaminergic nigrostriatal system (motor and sensorimotor integration deficits) (Fernagut et al. 2003; Fernagut et al. 2002) and (iii) the hypothalamo-infundibular system (decreased growth hormone and prolactin secretion) (Bosse et al. 1997). An obvious phenotype observed in mice lacking DAT is the remarkable increase in their spontaneous locomotor activity during both day and night cycles (Giros et al. 1996). This increase is of the same magnitude as in normal mice treated with very high doses of amphetamine and cocaine, which are known to produce this locomotor effect by increasing the amount of striatal DA (Giros et al. 1996).

Besides providing strong direct evidence for a role of the DAT in the tight control of DA homeostasis and transmission, DAT-KO mice have provided key elements in understanding the way psychostimulants act on the DA system.

Behaviorally, DAT-KO mice do not respond to cocaine and amphetamine, when these drugs are given in their home cages, at doses that produce marked increases in locomotor activity and stereotyped behaviors in normal animals (Giros et al. 1996).

These findings are consistent with cyclic voltammetry data which shows that, in the absence of the DAT, amphetamine is completely ineffective in promoting release of DA despite being able to abolish intracellular stores of the neurotransmitter demonstrating the necessity of the DAT for the DA-releasing action of amphetamine (Giros et al. 1996). These conclusions have also been corroborated by results obtained from studies using short and long-term unilateral DAT antisense treatments in the SN of rats (Silvia et al. 1997). Indeed, the rotational behavior obtained in this model demonstrates that cocaine acts as a DAT blocker, whereas amphetamine acts as a DA releaser and this release is DAT-dependent.

Interestingly, DAT-KO mice were still able to express conditioned place preference (CPP) to cocaine (Sora et al. 1998), long term behavioral sensitization (Morice et al. 2010) and the ability to self-administer the drug, although less than control (Rocha et al. 1998). While DAT-KO still showed rewarding properties to amphetamine (Budygin et al., 2004), this psychostimulant was also able to significantly reduce the locomotor activity of the DAT-KO mice when given in a novel environment. This was also the case with methylphenidate (Gainetdinov et al. 1999). These findings lead to the conclusion that, in the absence of DAT, the rewarding properties of psychostimulants are maintained through their action on the noradrenaline transporter, which is present in the ventral parts of the NAc and that has in fact higher affinity to DA than the DAT itself (Carboni et al. 2001; Moron et al. 2002). These findings have lead to the proposal that DAT inhibition is dispensable for cocaine reward, at least in DAT-KO mice, and that redundant monoamine systems might mediate responses to cocaine.

The effects of drugs of abuse other than psychostimulants were also tested on DAT-KO animals. Alcohol for instance had similar effects in DAT-KO animals and control increasing extracellular level of DA by 80% thus indicating that the DAT is not

mandatory for the effects of alcohol on DA (Mathews et al. 2006). Morphine induced higher CPP, DA levels and accumbal c-fos levels in DAT-KO mice than control littermates further indicating that rewarding responses were still present and effective in these animal models (Mathews et al. 2006). In support of this are the findings with natural rewards demonstrating that the rewarding properties of a sucrose solution are higher in DAT-KO mice than controls (Rossi and Yin 2015).

Because of continuously increasing evidence for a role of endocannabinoids in reward processes (Solinas et al. 2008), endocannabinoid signaling was assessed in DAT-KO mice and the ability of endocannabinoid ligands to normalize behavioral deficits was evaluated, namely spontaneous hyperlocomotion (Tzavara et al. 2006). DAT-KO mice had reduced striatal anandamide levels and in these mice, anandamide reuptake inhibitors attenuated spontaneous hyperlocomotion. These results suggest that maintaining an endocannabinoid homeostasis might constitute an interesting avenue to explore to counter psychostimulant-induced hyperdopaminergia and potentially their behavioral consequences.

b. Manipulation DAT expression levels and drugs of abuse

Hyperdopaminergic mutant mice were also generated by reducing expression of the DAT to 10% of wild-type levels and are referred to as DAT-knockdown animals (Zhuang et al. 2001). These animals display hyperactivity, increased grooming, stereotypy and impaired response habituation in novel environments (Zhuang et al. 2001). Additionally, these mice show higher food intake and enhanced motivation to rewarding stimuli (Cagniard et al. 2006; Pecina et al. 2003) suggesting that motivation to work for a food reward may be under the critical influence of tonic dopaminergic activity.

Another model useful for determining how inhibiting the DAT may contribute to the effects of cocaine was generated with mice that express a cocaine-insensitive DAT (DAT-CI mice). These mice bear a DAT gene that has no binding site for cocaine but can still reuptake DA (Chen et al. 2006). In these mice, cocaine suppresses locomotor activity, does not elevate extracellular DA in the NAc, and does not produce reward as measured by CPP (Chen et al. 2006). In addition, these mice do not show any cocaine-induced spine density within the NAc (Martin et al. 2011). These results suggest that blockade of DAT is necessary for cocaine reward in mice with a functional DAT. However, these mice still maintain motivation to food reward and self-administer amphetamine (Thomsen et al. 2009). Viral-mediated re-expression of wild-type DAT in the rostrolateral striatum restored cocaine-induced locomotor stimulation and sensitization in DAT-CI mice (O'Neill et al. 2014). In contrast, the expression of wild-type DAT in the DSt, or in the medial NAc, did not restore cocaine-induced locomotor stimulation. This indicates that DAT-inhibition in the rostrolateral striatum alone is sufficient for cocaine's locomotor stimulating effect.

A recent study has used mice with different DAT expression levels: constitutive DAT knockdown (with ~5% of wild-type DAT expression levels), DAT knockdown heterozygotes (with ~50% of wild-type DAT expression levels) and inducible DAT knockdown mice, all compared to wild-type animals (Cagniard et al. 2014). The authors tested whether the effects of cocaine and amphetamine, because of their different mechanisms of actions, would be affected differently by changes in DAT expression levels. The results obtained clearly indicated that there are both presynaptic and postsynaptic mechanisms involved in differential responses to cocaine and amphetamine in relation with DAT expression levels (Cagniard et al. 2014). In other words, responses to cocaine and amphetamine seem to depend both

on psychostimulant drug doses and DAT expression levels. For instance, mice with low DAT expression levels were more sensitive to further DAT blockade by small doses of cocaine. In contrast, reduced DAT level reduced amphetamine-induced DA release through reversal of DAT, and thus reduce sensitivity to this drug (Cagniard et al. 2014).

Researchers have also generated transgenic mice overexpressing DAT (DAT-tg) which have a 3-fold increase in DAT protein levels resulting in a 40% reduction of extracellular DA concentration in the striatum (Ghisi et al. 2009). As expected, these mice have increased levels of striatal D1 (30%) and D2 (~60%) DA receptors levels and 300% increase in the basal levels of phospho-Akt in the striatum, indicative of the reduced extracellular DA tone in these animals. Behaviorally, DAT-tg animals showed increased climbing behavior after stimulation with either apomorphine or a co-administration of selective D1- and D2-receptor agonists. They also showed markedly increased locomotor responses to amphetamine accompanied by a 3-fold greater increase in the amount of DA released by amphetamine (Salahpour et al. 2008). In contrast with mice with no or low levels of DAT, overexpression of DAT resulted in reduced operant responding for natural rewards (Salahpour et al. 2008).

The val 559 mutation is a nonsynonymous single nucleotide polymorphism (SNP), converting Ala559 to Val (A559V) in the coding region of the DAT and that was found to be associated in humans with bipolar disorder and ADHD (Grunhage et al. 2000). Cells carrying this mutation show normal DAT levels, normal presence of the DAT at the membrane and normal reuptake of DA (Mazei-Robison et al. 2005). Mice baring this mutation show elevated extracellular DA levels and less behavioral response to amphetamine with no changes in spontaneous locomotor activity (Mergy et al. 2014).

DAT contains a C-terminal PDZ (PSD-95/Discs-large/ZO-1) domain-binding sequence believed to bind synaptic scaffolding proteins (Torres et al. 2001). Disruption of PDZ domains in mice has been performed and result in almost complete loss of DAT expression mirrored by a spontaneous hyperactivity and reduced response to amphetamine (Rickhag et al. 2013). These results clearly support the proposal that PDZ domain interactions are critical for synaptic distribution of DAT *in vivo* and thereby for proper maintenance of DA homeostasis and responses to psychostimulants.

Genetic manipulation of DA receptors

The ability to make genetic changes in a predetermined way has provided an invaluable new tool to study individual players of dopaminergic transmission (Le Foll et al. 2009). Pharmacological manipulations using the psychostimulants cocaine and amphetamine have suggested that it is mainly the D1R that mediates the molecular and behavioral effects of these drugs (Kalivas and Stewart 1991). This has been confirmed using D1R-KO mice that show no further increase in their locomotor response to high doses of cocaine (Xu et al. 1994). In fact their locomotor response is decreased following psychostimulant treatment and this may be due to the contribution of the serotoninergic pathway in regulating locomotor activity (Xu et al. 1994). Additionally, D1R-KO animals show no deficits in acquisition of cocaine-induced CPP (Miner et al. 1995) but do not self-administer cocaine further indicating that the D1R is critical for the reinforcing effects of cocaine (Caine et al. 2007). Interestingly, food reinforcement is maintained at normal levels in these animals (Caine et al. 2007).

The role of the D1R subtype in alcohol-seeking behaviors was studied in D1R-KO mice (El-Ghundi et al., 1998). Voluntary ethanol consumption and preference over water are markedly reduced in these animals as compared to heterozygous and wild-type controls (El-Ghundi et al. 1998). This is also the case when transgenic animals are offered a single drinking tube containing alcohol as their only source of fluid. D1R blockade with SCH-23390 effectively reduced alcohol intake in control mice to the level seen in untreated D1-KO mice. D2R blockade with sulpiride caused a small but significant reduction in alcohol intake and preference in wild type mice and only slightly attenuated residual alcohol drinking in D1R-KO mice (El-Ghundi et al., 1998). This demonstrate that the D1R has a key role in the motivation for alcohol consumption

Interestingly, inactivation of the D2 gene produced almost the opposite phenotype in the mutant mice. D2R-KO mice are akinetic and bradykinetic with significantly reduced spontaneous movement, a phenotype that resembles that observed with specific D2 antagonists as well as in extrapyramidal syndromes of Parkinson's disease (Baik et al. 1995). In a cocaine self-administration paradigm, when high doses of cocaine on the descending part of the cocaine dose-effect function were available, D2R-KO mice self-administered at higher rates than their heterozygous or wild-type littermates, but the ascending limb of the cocaine dose-effect function did not differ between genotypes (Caine et al. 2002). In addition, D2-like antagonist eticlopride increased rates of high doses of cocaine self-administration in wild-type but not in D2R-KO mice (Caine et al. 2002). Collectively, these findings suggest that although D2R is not necessary for cocaine self-administration, it is involved in some mechanism that seems to limit the rates of self-administration of high-dose of cocaine. This is in line with findings showing that the DA-releasing effects of

psychostimulants seem to be higher in these KO mice, suggesting that lower doses may produce higher effects (Rouge-Pont et al. 2002).

In an operant ethanol self-administration using a continuous access procedure, D2R-KO mice display lower ethanol-lever responding compared to wild-type mice (Risinger et al. 2000). Food lever responding and water intake were the same in both genotypes (Risinger et al. 2000). Under conditions that produced reliable place preference to ethanol in both wild-type and heterozygous (HET) mice, D2R-KO mice show no evidence of place conditioning (Cunningham e al., 2000) supporting the hypothesis that DA D2 receptors is involved in ethanol reward in mice.

The rewarding properties of morphine in the CPP paradigm are completely absent in D2R-KO mice but morphine withdrawal is unchanged in these mice (Maldonado et al. 1997). Food-induced CPP was still expressed in these animals (Maldonado et al. 1997). The ability of intravenously delivered morphine to maintain lever pressing in these mice was studied under fixed ratio 4 (FR4) schedule and a progressive ratio (PR) schedules (Elmer et al. 2002). D2R-KO mice did not respond more to morphine than to saline and did not respond more when increased ratios were required by the PR schedule. Thus, morphine failed to serve as a positive reinforcer in the D2R-KO mice indicating that the rewarding effects of morphine appear to depend critically on an intact D2R system.

D3R-KO mice showed higher basal locomotor activity levels in comparison with wild-type mice and ethanol produced similar magnitudes of CPP in both genotypes (Boyce-Rustay and Risinger 2003; McQuade et al. 2003). In a two-bottle drinking procedure, no difference was found between D3R-KO and wild-type mice in either alcohol consumption or preference (Boyce-Rustay and Risinger 2003; McQuade et

al. 2003). In an operant self-administration procedure D3-KO and wild-type mice had similar response rates to ethanol or food as well as similar water intakes (Boyce-Rustay and Risinger 2003; McQuade et al. 2003). Overall, these results indicate that D3R is not involved in either ethanol reward or intake. In contrast, D4R-KO mice displayed supersentivity to ethanol (Rubinstein et al. 1997) as well as to psychostimulants (Katz et al. 2003). Indeed, cocaine was a more potent stimulant of locomotor activity in D4R-KO mice compared to wild-type littermate. In addition, cocaine was more potent in producing discriminative-stimulus effects in D4R-KO mice further suggesting a role of the D4R in vulnerability to stimulant abuse (Katz et al. 2003).

Finally, D5R-KO mice show normal cocaine discrimination and normal dose response activity (Elliot et al. 2003). However, cocaine dose-dependently stimulated activity at higher levels in D5R-KO mice compared to control indicating an involvement of D5R in the locomotor stimulant effects of cocaine but limited involvement in the discriminative-stimulus effects of this drug (Elliot et al. 2003).

Vulnerability to addiction

It is evident that people are not equal in relation to the risks of becoming addicts. Indeed, whereas most people try and consume drugs sporadically, only 10-30% develop an addiction over time (Everitt et al. 2008; Kreek et al. 2005; Marinelli and Piazza 2002; Piazza and Le Moal 1996; Deroche-Gamonet and Piazza 2014; Solinas et al. 2010b). This differential vulnerability is due to complex interactions between genetic factors, the effects of the drug and the environment (Deroche-Gamonet and Piazza 2014; Solinas et al. 2010b; Kreek et al. 2005; Renthal and Nestler 2008). The term environment here actually includes a great number of factors from socio-economical factors, to family and peer relations, life events, exposure to pollutants

and medications. These factors participate in shaping the personality and characters of individuals, in determining the socio-cultural context that favors or not drug taking but they also influence the effects of drugs and their ability to interact with neuronal circuits and to produce neuroadaptations. Since evidence that genetic manipulations of the dopaminergic system influence the response to addictive drugs has been reviewed above, in the following section we will focus on the effects on addiction of environmental manipulations.

Environment, DA and vulnerability to addiction

Epidemiological data and experimental data clearly demonstrate that environment plays a major role in the vulnerability to addiction (Renthal and Nestler 2008; Solinas et al. 2010b; Kreek et al. 2005; Stairs and Bardo 2009; Sinha 2007, 2008; Koob 2008). Indeed, people with genetic predisposition will not necessarily develop addiction if they are exposed to positive environments and, in contrast, people with genetic resistance to drugs may develop addiction if they are exposed to negative environments.

In humans, the definition of positive or negative environment can be established "*a posteriori*". All environmental conditions that increase the risk of addiction are considered negative and, conversely, all environmental conditions that decrease the risk of addiction are considered positive (Jessor and Jessor 1980; Kodjo and Klein 2002). One of the most common factors in negative environmental conditions is the exposure to life stress and trauma that greatly increase the risk to develop addiction (Koob 2008; Piazza and Le Moal 1996; Sinha 2001; De Bellis 2002). In contrast, good family and peer relationships, a stable, understanding and loving entourage but

also physical and mental stimulation decrease the risk of addiction (Jessor and Jessor 1980; Kodjo and Klein 2002; Solinas et al. 2010b; Pang et al. 2018).

In animal models, negative environment is always mimicked by exposure to stress, which may be more or less intense, more or less “early” and more or less chronic (Goeders 2002; Koob 2008; Piazza and Le Moal 1996). In contrast, positive environment is mostly mimicked by environmental enrichment, which is an environment design to facilitate social stimulation, curiosity, cognition and physical exercise (Pang et al. 2018; Solinas et al. 2010b; Stairs and Bardo 2009). Using these two types of manipulation a considerable amount of literature has established that stress indeed increases whereas environmental enrichment reduces the risk to develop and maintain an addiction (Renthal and Nestler 2008; Solinas et al. 2010b; Kreek et al. 2005; Stairs and Bardo 2009; Sinha 2007, 2008; Koob 2008).

Several lines of evidence suggest that the DA system is involved in environment-mediated alteration of vulnerability to addiction (Nader et al. 2008; Goeders 2002; Piazza and Le Moal 1996; Solinas et al. 2010b). For example, a seminal study by the group of Michael Nader showed that, in non-human primates, changes in social ranking influence levels of DA D2Rs in the striatum with dominant individuals showing less D2R than subordinates and self-administrating less cocaine (Morgan et al. 2002). In addition, it has been clearly established that stress produces alterations in the DA system that increase the reinforcing effects of drugs (Goeders 2002; Koob 2008; Piazza and Le Moal 1996; Ungless et al. 2010). Conversely, exposure to environmental enrichment produces changes in the DA system that may be related to decreased vulnerability to addiction (Bezard et al. 2003; El Rawas et al. 2009; Kim et al. 2016; Solinas et al. 2010b; Solinas et al. 2009; Thiriet et al. 2008; Lafragette et al. 2017). However, this effect may be mostly related to post-synaptic changes because

drug-induced release of DA in the ventral striatum is not affected by environmental enrichment (El Rawas et al. 2009; Solinas et al. 2009).

Addiction to DA replacement therapy medications in Parkinson's disease

A particular phenomenon that provides support for the role of DA in addictive behavior is the development of addiction to dopaminergic medications in people suffering from Parkinson's disease (PD). PD is characterized by the degeneration of several neuronal ensembles including mesencephalic dopaminergic neurons in the SN and to a lesser extent in the VTA (Chinaglia et al. 1992). DA loss leads to basal ganglia dysfunction and the expression of a parkinsonian syndrome characterized by the variable association of several motor symptoms (akinesia/bradykinesia, rigidity, tremor and postural instability). Management of motor symptoms in PD is achieved with DA replacement therapy (DRT), which includes the DA precursor L-dopa and DA agonists. Chronic intake of DRT can lead to a number of motor and non-motor side effects with severe consequences on the quality of life of the patients and their caregivers (Bastide et al. 2015). Motor side-effects are characterized by several types of motor fluctuations ranging from erratic changes in mobility to abnormal involuntary movements defined as L-dopa induced dyskinesia and that manifest with chorea, dystonia and ballism (for review, see (Bastide et al. 2015)). Non-motor side effects of DRT encompass various abnormal behaviors such as punding or hobbyism (stereotyped/repetitive behaviors), impulse control disorders (behavioral addictions such as pathological gambling, binge eating, hypersexuality or compulsive shopping) as well as the DA dysregulation syndrome (DDS), which is characterized by the compulsive use of DRT (for reviews, see (Voon et al. 2009; Voon et al. 2017)). Compulsive use of DRT is characterized by excessive intake of dopaminergic

medications by the patient, which in turn leads to the emergence or worsening of L-dopa induced dyskinesia, impulse control disorders, as well as hypomania and psychosis (Giovannoni et al. 2000).

Compulsive use of DRT had been occasionally described since the introduction of L-dopa (Nausieda 1985), but more recently it has become the subject of specific attention to precisely define the clinical syndrome, its prevalence, and the profile of affected PD patients (Giovannoni et al. 2000; Pezzella et al. 2005). Giovannoni and colleagues provided a detailed investigation of patients presenting with compulsive use of DRT, and reported that males with a younger age at disease onset were more likely to suffer from DDS (Giovannoni et al. 2000). DDS has an estimated prevalence of 3-4% of PD patients (Giovannoni et al. 2000; Pezzella et al. 2005). Specific diagnosis criteria were also defined based on DSM criteria for substance dependence with additional items specific to PD (Giovannoni et al. 2000). DDS is mainly associated with L-dopa or some DA agonists (essentially apomorphine and bromocriptine). Patients start to self-medicate and rapidly increase their intake of DRT in excess of what would be sufficient to relieve parkinsonism. Patients suffering from DDS display an altered perception of their motor status, feeling relieved from motor symptoms only when they are highly dyskinetic (Giovannoni et al. 2000; Lawrence et al. 2003). Over 90% of PD patients suffering from DDS indeed display drug seeking behavior and escalation of L-dopa intake (Warren et al. 2017). They rapidly consume the amount of prescribed DRT, and then they engage in pathological drug seeking and hoarding to maintain adequate drug supply (Warren et al. 2017). Such massive intake of DRT then leads to the emergence of several behavioral disorders. These include an occurrence of severe dyskinesia, as well as behaviors such as punding (stereotyped, repetitive behavior initially described in

methamphetamine abusers), hobbyism, walkabout, hypersexuality, pathological gambling or shopping (Giovannoni et al. 2000).

Because addiction to DRT shares several features with psychostimulant addiction, this syndrome was discussed in relation with several theories/models of psychostimulant addiction (Lawrence et al. 2003). DDS was initially described as a type of hedonistic homeostatic dysregulation (Giovannoni et al. 2000), with reference to the model proposed by Koob and Le Moal (Koob and Le Moal 1997), where three components (anticipation/preoccupation of drug intake, binge intoxication and negative affect occurring during drug withdrawal) of a spiraling cycle become progressively dysregulated due to sensitization and counter-adaptation processes. In the hedonistic homeostatic dysregulation model, the negative affective state occurring during withdrawal is an important contributor to the addiction cycle and tapering or cessation of L-dopa administration can lead to a negative affective state in over 60% of patients (Warren et al. 2017). Importantly, in the specific context of PD, this negative state is due not only to the symptoms of drug withdrawal but also to the resurgence of the parkinsonian symptoms as the treatment is stopped. However, a withdrawal syndrome has also been described in the tapering of the treatment with DA agonists in PD patients displaying impulse control disorders (Rabinak and Nirenberg 2010), even though these patients do not display compulsive drug intake.

DDS can also be viewed as a form of incentive sensitization, according to the theory developed by Robinson and Berridge (Robinson and Berridge 1993) that posits that sensitization of neural circuits involved in the processing of incentive salience results in an increased valence of drug-associated cues and stimuli. In this model, sensitization leads to an increased motivation (wanting) for the drug but not to increased pleasurable effects of the drug (liking) (Robinson and Berridge 1993).

Clinical and neuroimaging evidence suggest that incentive sensitization is involved in DDS since patients report increased “wanting”, but not “liking” the drug, and this “wanting” is correlated with increased DA neurotransmission in the NAc (Evans et al. 2006).

Unlike psychostimulant addiction, which results from the initially voluntary intake of drug in neurologically intact subjects, DDS involves the medical prescription of drugs that act on a brain already displaying severe alterations of DA homeostasis (and other neurotransmitters) due to the degenerative process of PD. How the degenerative process, DRT and specific vulnerability trait interacts in the specific context of DDS remains largely unknown. With regards to the rewarding effects of DRT, L-dopa and DA agonists seem to possess different properties. Administration of L-dopa to healthy subjects is not associated with pleasurable or psychostimulant effects (Liggins et al. 2012), while PD patients (particularly those suffering from DDS) report feelings of pleasure, well-being and a psychostimulant effect when on L-dopa (Castrioto et al. 2013), suggesting that dopaminergic neurodegeneration may be required for the expression of psychostimulant-like properties of L-dopa. This hypothesis was confirmed in an animal model of PD where L-dopa displayed rewarding properties and decreased the palatability of a non-drug reward only in rats with a bilateral lesion of the SN (Engeln et al. 2013). Conversely, DA agonists such as apomorphine, bromocriptine or pramipexole display rewarding properties in normal rats (Hoffman et al. 1988; Riddle et al. 2012; van der Kooy et al. 1983). However, the rewarding properties of apomorphine and pramipexole are increased in animals with a lesion of the SN (Campbell et al. 2014; Riddle et al. 2012). Collectively, these studies indicate that the different classes of DRT display specific rewarding properties that are increased following nigral dopaminergic degeneration.

Several neuroadaptations consecutive to the dopaminergic denervation may be involved. These include the supersensitivity of post-synaptic DAR, desensitisation of D2 autoreceptors, as well as overstimulation due to DRT in conjunction with the remaining endogenous dopamine in the brain regions that display low levels of dopaminergic denervation, an effect named “DA overdose”.

Neuroimaging studies provide some support to the DA overdose theory (Cools et al. 2001; Swainson et al. 2000). Using displacement of raclopride binding as an index of L-dopa-induced DA release, PD patients suffering from DDS were found to display an enhanced L-Dopa-induced reduction of raclopride binding in the ventral striatum, thereby suggesting a sensitization of DA transmission in this striatal subregion (Evans et al. 2006). Interestingly, a similar sensitization was also found in the putamen of PD patients displaying L-dopa induced dyskinesia (de la Fuente-Fernandez et al. 2000; de la Fuente-Fernandez et al. 2004), suggesting that both motor and non-motor side effects of L-dopa may share some common neurobiological mechanisms. Whether the altered synaptic plasticity and associated dysregulation of intracellular signaling occurring in L-dopa induced dyskinesia are recapitulated in DDS remains to be determined.

DA and the treatment of addiction

Given the vast literature about the critical role of DA in drug addiction, as it should be expected, extensive research has been conducted on the use of dopaminergic compounds for the treatment of drug addiction. For example, blocking DA neurotransmission was expected to block the reinforcing effects of drugs and therefore, to reduce addiction-related behavior. However, so far accumulating evidence suggests that dopaminergic antagonists are not effective to treat drug addiction (Alvarez et al. 2013; Verrico et al. 2013). The reasons for this partial failure

are multiple. First of all, although DA appears to play an important role in addiction to all drugs, it is clear that its role is much more critical for psychostimulants whereas the role in opiate, nicotine, alcohol and cannabis abuse is much less central (Pierce and Kumaresan 2006; Nutt et al. 2015). A second aspect that should be taken into consideration is that pharmacological blockade could be overwhelmed by increasing the amount of drug consumed. Indeed, studies in animals and humans show that, under most conditions, blockade of DAR increases drug self-administration as individuals try to compensate for the reduction of the effects of unitary doses (Arnold and Roberts 1997; Koob et al. 1997; Mello and Negus 1996) and similar results have been found in humans (Haney et al. 2001). Thus, in naturalistic settings, humans would have the possibility to counteract the effects of DA blocked by increasing the dose of the drug. Thirdly, whereas DA system is arguably the major actor in reward process, reward processes only constitute a part of the addiction pathology (Koob and Volkow 2010, 2016; Volkow et al. 2016). Indeed, as discussed earlier positive reinforcement is critical for the development of addiction but upon repeated administration, conditioned effects of drugs and habits start playing a major role (Everitt and Robbins 2005; Koob and Volkow 2010, 2016; Volkow et al. 2016). Although DA also plays role in conditioned effects and habits, these phenomena appear to be much more resistant to DA blockade than simple reinforcement (Everitt et al. 2008; Everitt and Robbins 2005). Fourthly, the cyclic nature of addiction pathology implies that phase of active self-administration and elevated DA levels are alternated with phase of abstinence and lower levels of DA that may be associated with anhedonia and craving (Koob and Volkow 2010, 2016; Volkow et al. 2016). Therefore, DA antagonist may well exacerbate negative affective states and increase negative reinforcement, which could lead to low tolerance and compliance for the

medication, cessation of the treatment and finally relapse (Dackis and Gold 1985; Koob and Volkow 2010, 2016; Kuhar and Pilotte 1996). Indeed, most medication with selective blockade of DA receptors used in clinical settings, which are mostly D2 antagonists, are known to produce aversive psychological effects that reduce their compliance (Alvarez et al. 2013). With this in mind, antipsychotic medications with mixed pharmacological profile comprising both D2 blockade and effects on other targets such as serotonin 5-HT2 receptors (Alvarez et al. 2013). However, a meta-analysis of the studies using these compounds has also concluded that their effectiveness in the treatment of addiction is very limited (Alvarez et al. 2013). Importantly, the use of selective D1-receptor antagonists for clinical applications has been hampered by issues with bioavailability, binding affinity, pharmacological kinetics, and side effects but new pharmacological compounds may provide novel tools for the pharmacotherapy of addiction (Kim et al. 2015). The use of the selective D1 antagonist, ecopipam, has been tested on self-administration of cocaine, in humans but it was found that its administration increased self-administration of cocaine while decreasing cocaine craving (but in the same patients craving for alcohol and tobacco smoking increased) suggesting that it is unlikely to be an effective treatment for cocaine addiction (Haney et al. 2001). Some authors have proposed that signaling of D1R may be modulated by interacting targeting second messengers, allosteric modulators, or by making targeted modifications to D1R machinery (Kim et al. 2015). However, lessons from the use of naltrexone for opiate addiction suggest that therapy with antagonists may be effective only in a limited number of circumstances and mostly in very motivated people receiving long periods of high level of counseling (Blanco-Gandia and Rodriguez-Arias 2018). It should be noted that because of their specific neurobiological characteristics, several authors

have proposed targeting the D3R with antagonists and partial to better management of addiction (Newman et al. 2012; Le Foll et al. 2014). However, no conclusive evidence has been provided by clinical trials (Le Foll et al. 2014)

The case for the use of dopaminergic agonists in the management of addiction to psychostimulants is much stronger (Herin et al. 2010) and it is supported by parallels in opiate and nicotine addiction in which substitution therapy with opioid agonists such as methadone and buprenorphine (Dematteis et al. 2017) and nicotine replacement therapy (Haustein 2000; Etter and Stapleton 2006) have been proven to be relatively effective. Direct agonist of dopaminergic receptors do not appear to present the best pharmacological profile, do not appear to stimulate the reward system strongly enough and may produce unwanted effects such as impulsivity (Kim et al. 2015). Thus, most interest has been given to the investigation of indirect DA agonists that act on dopaminergic (and other monoaminergic) transporters. Among these drugs modafinil, bupropion, methylphenidate and slow release formulations of amphetamine and methamphetamine, that are used in humans for the treatment of other psychiatric disorders, have been tested in humans and although some studies have found some beneficial effects of these compounds the overall effects have been limited (Herin et al. 2010; Verrico et al. 2013). New avenues for this therapeutic strategy may arise from the development of new synthetic blockers of DAT that bind to the transporter without producing the psychotropic and reinforcing of cocaine and amphetamine (Rothman et al. 2008).

It should be finally mentioned that other indirect strategies to boosting dopaminergic activities such as decrease metabolism by the MAO antagonist selegiline or increase

in DA precursors such as administration of DOPA and carbi-DOPA have been tested but have shown limited success (Herin et al. 2010; Verrico et al. 2013).

Altogether these studies show that notwithstanding the high expectations on the possibility to target the DA system for the treatment of addiction, until now the results have not met these expectations (Nutt et al. 2015). However, the quest for new effective DA medications continues by refining of the elements in the DA system to target and the specific conditions in which these medications may be effective.

Conclusions

We know a lot, arguably more than any other neurotransmitter, about the role of DA in addiction. Although this knowledge has not translated in medications as it could have been hoped (Nutt et al. 2015), the experience with DA may be an exemplary showcase of the role of research (preclinical and clinical) in shedding light into brain functioning. In the attempt to understand drug addiction, not only we have produced considerable advances in the understanding of how brain DA functions in ways that are helpful for different neurological and psychiatric disorders, but this knowledge has also been used to predict vulnerability, effectiveness of the treatment and recovery from addiction. More importantly, the failure of some of the predictions of the original DA-driven hypotheses have allowed the field to re-conceptualize addiction as a complex disorder with different aspects and different phases (Koob and Volkow 2010), to consider that different drugs may be associated with different addiction-related behaviors (Badiani et al. 2011) and to question the validity of established animal models addiction and their ability to predict effectiveness of new medications in humans and to develop new ones (Pierce et al. 2012). Finally, the humbling reality of the difficulties in translating the best preclinical and clinical knowledge into new effective treatments should teach researchers and the general public to accept that

the path from research to real-life applications is arduous, unpredictable and slow and that even the most promising discoveries may need considerable time and energy to lead to meaningful clinical results.

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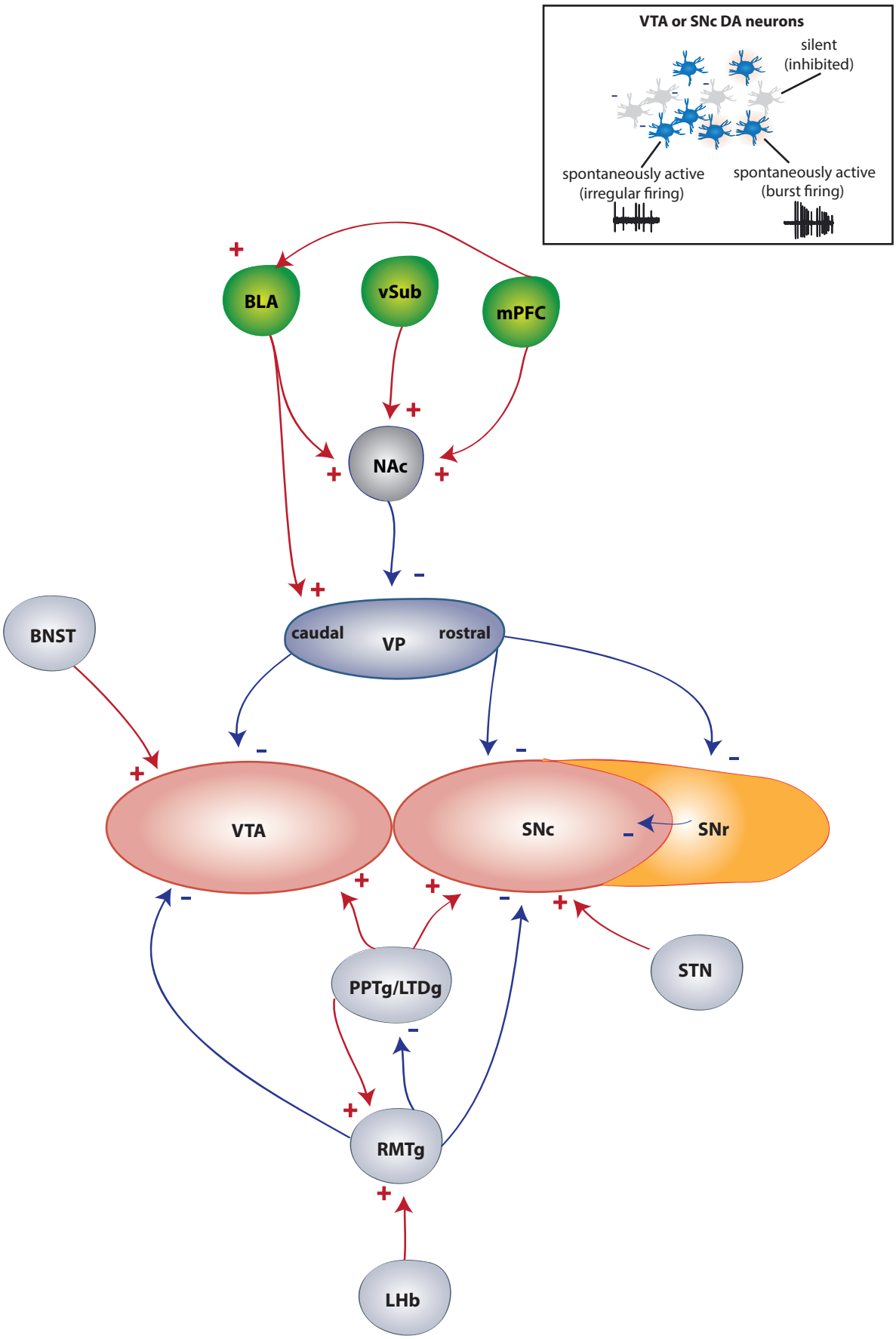
Figure 1- Simplified schematic representation of the afferent regulation of DA neurons in the VTA and the SNc. Inset – Activity population of DA neurons. About half of VTA neurons are firing spontaneously, and only neurons that fire spontaneously can fire in bursts of action potentials, due to activation of PPTg afferent. Abbreviation: VTA, ventral tegmental area; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; BLA, basolateral amygdala, vSub, ventral subiculum of the hippcampus; mPFC, medial prefrontal cortex, NAc, nucleus accumbens; VP, ventral pallidum; STN, subthalamic nucleus;PPTg, pedunculopontine tegmental nucleus; LDTg, lterodorsal tegmentl nucleus; RMTg, rostromedial tegmental nucleus; LHb, lateral habenula.


VTA or SNc DA neurons
silent
(inhibited)
spontaneously active
(irregular firing)
spontaneously active
(burst firing)
BLA
vSub
mPFC
NAc
BNST
caudal
VP
rostral
VTA
SNc
SNr
PPTg/LTDg
STN
RMTg
LHb