The Molecular Neurobiology of Addiction

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Abstract

Addiction, a severe chronic substance use disorder, represents one of the biggest health problems facing society today and consists of a shift from impulsivity to compulsivity with regards to drug-taking. Behaviorally, it is characterized by a three-phase cycle of intoxication, withdrawal and preoccupation-anticipation. Research into the neurobiology underlying this behavioral cycle has focused on changes in dopaminergic activity within mesocorticolimbic projections of the reward circuit. However, this focus has yielded therapeutic and prevention strategies with both limited efficacy and application. Recent advances in the field have highlighted several other neurotransmitter and biological systems that may be involved in the etiology of substance use disorders. In the following chapter, the major modifications of the dopaminergic system involved in addiction are presented, before shining light on the contributions of the endocannabinoid, as well as the immune and stress systems. The pathophysiology of each system is discussed in the context of each phase of the addiction cycle. Specific receptors and transcription factors are highlighted as potential molecular targets for intervention strategies within addiction. Finally, a shift of focus from the sole contribution of the dopaminergic circuit, onto the reciprocal relationships between and synergic contributions of each of the aforementioned systems is proposed for future research.

Glossary

MSNs: medium spiny neurons, inhibitory GABAergic neurons representing 95% of the nucleus accumbens cell population.

eCB-LTD: endocannabinoid-mediated long-term depression, a type of plasticity leading to weakening of synapses.

CB_1R-LTP: cannabinoid receptor type 1-dependent logn-term potentiation, a type of plasticity leading to strengthening of synapses.

Cdk5: cyclin-dependent kinase 5, enzyme required for proper brain development.

HMGB1: high motility group box 1, may bind RAGE and interacts with TLR4 in signal transduction pathway.

Positive/negative reinforcement: associative learning process where a behavior will be linked with a reward (positive consequence) or a punishment (negative consequence), which will determine whether the behavior will occur or not in the future.

Keywords

Addiction, dopamine, endocannabinoids, HPA axis, inflammation, stress, substance use disorders.

1. Introduction

Addiction to alcohol or illicit drugs is defined as a severe and chronic substance use disorder, where there is a shift from impulsivity to compulsivity in drug-taking. Substance use disorders affect up to 16% of the population for alcohol, and up to 3% for drugs (World Health Organization, 2004a, 2004b). Mental health services are the most solicited for treatment of alcohol and drug use disorder, which are often comorbid with other mental health disorders, such as major depressive disorder, bipolar disorder, or anxiety disorders (Harris et al., 2019). Overall, such comorbidities make the study of addiction quite complicated as they prevent clear distinctions between behavioral and biological mechanisms uniquely associated to this brain pathology.

The research into preventive and therapeutic strategies targeting addiction is further complicated by the intricate relationship between the behavioral manifestations and the associated underlying biological mechanisms. On a behavioral level, addiction can be conceptualized as a three-phase cycle, starting with the intoxication phase, and followed by the withdrawal and preoccupation-anticipation phases, which is when drug-taking becomes chronic and addictive. Each of these phases is characterized by specific neurobiological changes in the reward circuit, the mechanisms of which are still under scrutiny. Scientists have mainly focused on distinct dopaminergic changes underlying the experience of pleasure and reward, however, several other neurotransmitter systems, such as the endocannabinoid (eCB) system, as well as biological systems, including the immune system and hypothalamic-pituitary-adrenal (HPA) axis, have emerged as additional pathophysiological mechanisms involved in addiction.

In this chapter, we will first provide an overview of the behaviors and the underlying circuits associated with each of the three phases of the addiction cycle, and subsequently discuss,

for each phase, candidate neurotransmitter and biological systems underlying the occurrence and maintenance of that specific behavior.

2. The three-phase cycle of addiction

As mentioned above, addiction consists of three main phases: intoxication, withdrawal and preoccupation-anticipation. Together, these phases constitute an important framework in addiction research, as each of them are characterized by dysfunction of distinct brain circuits.

The first phase of addiction, *intoxication*, is the one where the individual is starting to expose himself to consumption of an addictive drug. This phase is characterized by an initial increased activation of the reward circuit, which ultimately leads to associative learning between drug-taking behavior and the pleasant sensation it evokes, a sensation which is triggered by the reward signal. This signal is generated through excitatory projections from the ventral tegmental area (VTA) to the nucleus accumbens (NAc), two of the most important brain structures eliciting reward (Volkow and Morales, 2015). Instead, in the second phase of addiction, also called *withdrawal*, the motivation and reward systems become desensitized due to repeated exposure to the drug. As the drug exposure becomes more frequent, the reward circuit becomes increasingly less reactive to stimulation (Koob and Le Moal, 2005). Furthermore, the withdrawal phase is marked by changes in the limbic system, in particular the amygdala and the ventral hippocampus, which together contribute to the formation of reward- and fear-related memories (Parsons and Hurd, 2015). Finally, in the third phase, called *preoccupation-anticipation*, fear-related memories lead to preoccupation of the drug reward, and is often associated with craving. At this stage, circuits in the prefrontal cortex (PFC), responsible for specific executive functions, including

decision-making and inhibitory control, exert a weakened control on limbic regions (George et al., 2012; Rando et al., 2011). Ultimately, this leads to goal-directed behaviors aimed at obtaining reward-related substances, and increases the risk of relapse upon stress or reward-associated cue triggers, which could be, for example, an environment or sensations associated with the drug (Cooper et al., 2017; Koob and Volkow, 2016; Volkow and Morales, 2015).

3. The role of the dopaminergic system

Among the most studied neurotransmitter systems underlying behavioral dysfunctions through all phases of the cycle of addiction, the dopamine (DA) system (Figure 1) is known to mediate states ranging from acute reward to dependence. To this day, knowledge regarding the role of the DA system in addiction has had a profound impact not only on research, but also on pharmaceutical developments aimed at targeting each phase of the addiction cycle.

3.1. *Intoxication*

The main evidence for the involvement of DA in intoxication stems from the fact that nearly all drugs of abuse share the property of facilitating dopaminergic transmission in reward circuits, particularly between the VTA and NAc. The NAc is populated by medium spiny neurons (MSNs), categorized as expressing either D_1 or D_2 dopamine receptors (DRs). Activation of D_1Rs encodes for reward, whilst stimulation of D_2Rs is insufficient for drug reward and seems to encode for aversion, behaviorally resulting in avoidance (Volkow et al., 2017; Volkow and Morales, 2015). Repeated D_1R activation, therefore, creates positive reinforcement between reward-associated cues (such as drug paraphernalia or the environment in which the drug is consumed) and the resulting rewarding signal. DA increases sufficiently large to activate D_1Rs, such as those

triggered by psychostimulants, increase dopaminergic release between the VTA and NAc. This is strongly correlated to the reinforcing and euphoric effects of drugs (Balster and Schuster, 1973; Drevets et al., 2001). At the molecular level, DRs signaling modulates the probability of converging glutamatergic inputs to generate action potentials whilst silencing background firing. Thus, drugs activating reward regions, and therefore releasing DA acting upon D_1R, induce neuroplastic changes strengthening specific D_1-MSN inputs. This then drives circuit dysfunctions underlying maladaptive behaviors of addiction, such as increased reward-seeking (Volkow et al., 2017; Volkow and Morales, 2015). In fact, psychostimulants increase DA release by blocking DA transporters, while tetrahydrocannabinol (Δ^9-THC), the psychoactive compound of cannabis, and nicotine have modest dopaminergic effects (Barkus et al., 2011; Stokes et al., 2009). Overall, DA release plays an essential role in intoxication for most drugs, with perhaps the exception of nicotine and cannabis, as its repeated release in reward circuits favors D_1R over D_2R signaling, resulting in long-term positive reinforcement, or reward-seeking.

Interestingly, such neuroplastic changes in reward circuits seem to be sustained by DR signal transduction mechanisms. Specifically, via cyclic adenosine monophosphate (cAMP)-dependent pathways, stimulated by D_1R and inhibited by D_2R activation (Caine et al., 2002). Chronic drug use upregulates activation of cAMP response element-binding protein (CREB) in the NAc (Self et al., 1998; Terwilliger et al., 1991). This ultimately drives the expression of genes involved in suppressing the reward circuit which, when prolonged, can blunt the rewarding effects of psychostimulants (MacNicol, 2017). CREB, therefore, drives requirement for a larger stimulus to produce the same pleasurable effect, or tolerance (Dinieri et al., 2009; Larson et al., 2011). Amongst the genes upregulated by CREB and responsible for neuroplastic changes, is the transcription factor ΔFosB. In particular, ΔFosB upregulates glutamate receptor α-amino-3-

hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) subunit 2 (GluR2), cell division protein kinase 5 (Cdk5) and nuclear factor kappa-light-chain enhancer of activated B cells (NFκB). Their collective expression contributes to exaggerated sensitivity to rewarding effects of drugs of abuse, as well as to reduced aversion, or a reduced sense of dislike or opposition to the drug, and promotion of drug-seeking behavior. Overall, the transcription factors CREB and ΔFosB have been highlighted as possible molecules, alongside DA, driving neuroplastic changes in NAc-VTA reward projection and consequent positive reinforcement known to underlie the intoxication phase.

3.2. *Withdrawal*

After the intoxication phase, neuroplastic changes aiming to counteract the effects of the drug are observed in the dopaminergic system during acute withdrawal. In contrast to the intoxication phase where DA signaling is increased, tonic DA concentrations are decreased in the reward areas, such as the ventral striatum, during withdrawal, namely from psychostimulants (Rossetti et al., 1992; Weiss et al., 1992, 1996). These dysfunctions are thought to be caused by downregulation of striatal D_2R and D_3R, a mechanism aiming to reduce DA signaling in consequence to chronic drug-taking, which is known to trigger DA release (Lee et al., 2009; Volkow et al., 1990). For this reason, reward thresholds are said to be generally elevated in this stage and are thought to subsequently contribute to the vulnerability to relapse. This was observed, for instance, in patients with alcoholism, where D_2R/D_3R availability negatively correlated with craving during withdrawal (Heinz et al., 2005). However, while these changes are consistently noticed in alcohol and psychostimulant addiction, this is not the case for other drugs, which may indicate drug-dependent mechanisms, as for intoxication (Brown et al., 2012; Stokes et al., 2012).

3.3. *Preoccupation-Anticipation*

The preoccupation-anticipation phase is characterized by dopaminergic changes comparable, and in direct continuation, to, those observed in the withdrawal phase. Reduced DA signaling leads, here, to reduced activity of the PFC, anterior cingulate cortex, and orbitofrontal cortex (Black et al., 2010). Together, these are responsible for cognitive functions such as decision-making, control and flexibility (Volkow and Baler, 2015), and are associated with craving (Volkow et al., 2005). These changes might occur because chronic drug exposure decreases striatal D_2R signaling (Everitt et al., 2008) and contributes to the D_1R-D_2R MSN signaling imbalance, previously mentioned in the intoxication phase (Bock et al., 2013). However, in contrast to the withdrawal phase, where D_3Rs are reduced, upregulated D_3Rs enabling D_1R pathways have been suggested as an additional mechanism in the preoccupation-anticipation phase (Fiorentini et al., 2010). In fact, reward-associated increases in DA, typically mediated by D_1R, are still observed during craving, upon drug-associated cues for instance, even though these increases are attenuated in substance abusers (Volkow et al., 2006; Wong et al., 2006). Overall, evidence supports a blunted reactivity of the dopaminergic system occurring in consequence of withdrawal, eventually leading to dysfunction of structures responsible for behavioral control, and thus to craving or relapse.

4. The involvement of the endocannabinoid system

The reward circuit is also modulated, at least partly, by the eCB system (Figure 1) (Parsons and Hurd, 2015; Serrano and Parsons, 2011). Two types of cannabinoid receptors are currently known: cannabinoid receptor type 1 (CB_1R) and type 2 (CB_2R). In particular, CB_1Rs are densely expressed in brain regions involved in addiction including amygdala, NAc, VTA and PFC, suggesting the involvement of CB_1R in each phase of the addiction cycle.

4.1. *Intoxication*

Generally, enhancement of eCB signaling can stimulate reward and neuroplastic changes similar to those observed in dopaminergic circuits during intoxication. The effects of eCB signaling in mediating reward are related to CB_1R's role in fine-tuning the activity of VTA-NAc DA projections (Parsons and Hurd, 2015). As mentioned in the dopamine section, indirect D_2-MSN excitatory projections act to inhibit DA release in the VTA, driving aversion, whilst D_1-MSN promotes it, driving preference. The eCB system regulates this through CB_1R, which preferentially mediates the suppression of D_2-MSNs projections, compared with rewarding D_1-MSN projections. Through this mechanism, increased eCB signaling in the NAc increases approach behavior while reducing avoidance of the drug (Grueter et al., 2010; Kravitz et al., 2012). Supporting this, CB_1R agonists seem to facilitate the rewarding and reinforcing effects of drugs, including alcohol and nicotine, whilst reducing CB_1R signaling attenuates these (Panagis et al., 2014). CB_1R mediates increases in extracellular DA levels in the NAc (De Luca et al., 2014; Solinas et al., 2006), and increases in eCB signalling, via inhibition of degrading enzyme fatty acid amide hydrolase (FAAH), may achieve potentiation of nicotine and cocaine-driven reward in mice (Mereu et al., 2015). Overall, this evidence suggests that eCB signaling, via CB_1R, contributes to sensitization of mesolimbic DA responses after stimulant exposure, and therefore leads to reinforcing effects.

Over time, however, chronic cannabinoid exposure decreases CB_1R activity throughout the brain (Breivogel et al., 1999), mainly at GABAergic interneuron terminals of the hippocampus (Dudok et al., 2015). Behaviorally, this may drive memory deficits and cognitive impairments seen in humans following chronic cannabis use (Puighermanal et al., 2012). Chronic use of non-cannabinoid drugs also disrupts CB_1R expression in ventral striatum and cortical regions (Ceccarini et al., 2014; Hirvonen et al., 2013). Therefore, long-term substance abuse seems to lead

to a deficiency and dysfunction in eCB signaling throughout the brain possibly contributing to consequent negative emotional states.

4.2. *Withdrawal*

A growing body of work indicates that the eCB system plays an integral role in the response to stress. This system particularly contributes to HPA axis response termination and suppression of aversive memories (Morena et al., 2016; Ruehle et al., 2012). This indicates that eCB activity might be a key component of withdrawal, as this phase is characterized by increased stress responsivity, anxiety and depression (Koob and Kreek, 2007). In fact, the basolateral amygdala (BLA) and PFC, all regions involved in stress reactivity, show reductions in eCB signaling. This deficiency is associated with alcohol withdrawal-induced anxiety-like behavior (Henricks et al., 2017). Conversely, enhancement of eCB signaling via FAAH inhibition reverses increased anxiety-like behavior associated with nicotine and alcohol withdrawal (Bura et al., 2010; Cippitelli et al., 2011). In addition, eCB reuptake inhibitor AM404 attenuates depression-like behavior during nicotine withdrawal (Mannucci et al., 2011). Overall, evidence shows that reductions in eCB signaling are observed during withdrawal and result in negative affective symptoms, which can be overcome via pharmacological enhancement of eCB activity.

4.3. *Preoccupation-Anticipation*

As the eCB system mediates certain types of synaptic plasticity, its dysfunction may also be involved in the development of maladaptive plasticity underlying the preoccupation-anticipation stage of addiction. In particular, two types of neuroplastic changes contribute to relapse and occur in regions involved in executive control and cue-induced compulsive drug-seeking behavior, such as the hippocampus and NAc. On the one hand, eCB-mediated long-term depression (eCB-LTD) is facilitated after chronic drug use in the VTA and is diminished in other

regions, leading to weakened synapses. These include the inhibitory synapses of the striatum, as well as the excitatory synapses in the hippocampus and NAc (Adermark et al., 2011; Fourgeaud et al., 2004; Mato et al., 2004). Following this, dopaminergic signaling is increased, which impairs executive control and favors compulsive drug-seeking (Heifets and Castillo, 2009; Hoffman et al., 2003; Pan et al., 2008). On the other hand, alongside these eCB-LTD impairments, CB_1R-dependent long-term potentiation (CB_1R-LTP) strengthens synapses in the extended amygdala and may drive vulnerability to cue- and stress-induced relapse (Chye et al., 2019; Reisiger et al., 2014; Scherma et al., 2016). In fact, CB_1R agonists reinstate drug-seeking in animal models of relapse, while CB_1R antagonists attenuate reinstatement of psychostimulant-seeking behavior (Fattore et al., 2007; Serrano and Parsons, 2011; Vries and Schoffelmeer, 2005). Overall, dysfunction of eCB-mediated plasticity seems to drive deficits in executive control and responsivity to stress, mediating the transition to compulsive drug-taking and relapse, via mechanisms dependent on eCB-LTD and CB_1R-LTP.

5. The role of inflammation

Another major system implicated in the pathophysiology of addiction and known to interact with the eCB and stress systems, is the immune system (Figure 1). In particular, pro-inflammatory molecules and inflammatory signaling appear to contribute to behaviors characterizing each stage of the three-phase cycle.

5.1. *Intoxication*

Inflammatory dysregulations often accompany drug-taking and are unsurprisingly observed in brain regions of the reward circuit. One of these dysregulated molecules is the toll-

like receptor 4 (TLR4), together with downstream pathways which are well-researched during the intoxication phase. Following binge ethanol exposure, the TLR4 ligand high mobility group box 1 (HMGB1) is upregulated in the PFC (Crews et al., 2013; Vetreno and Crews, 2012). TLR4 also mediates ethanol preference and cocaine-conditioned place preference, behaviors indicating an association between the environment and the drug-induced reward (Montesinos et al. 2016; Pandey et al. 2015). TLR4 has been reported to influence these behaviors via increases in DA in the NAc and increases in pro-inflammatory cytokine interleukin 1 beta (IL-1β) in the VTA (Northcutt et al., 2015). Indeed, TLR4 signaling activates NFκB transcription factor, which sustains the transcription of cytokines including IL-1β, and which is activated upon ethanol consumption (Qin and Crews, 2012; Ward et al., 1996). As previously mentioned, NFκB activation is observed after cocaine exposure in the NAc and is also necessary to establish conditioned place preference (Ang et al., 2001; Russo et al., 2009). Overall, studies show that TLR4 and NFκB are key mechanisms driving the inflammatory changes in the intoxication phase of the addiction cycle.

5.2. *Withdrawal*

Generally, a comparable picture can be drawn for the withdrawal phase in terms of inflammation. Behaviors associated with withdrawal are also related to TLR4-dependent inflammatory signals. Namely, withdrawal anxiety and depressive-like symptoms have been shown to be sensitized by LPS (Breese et al., 2008), a TLR4 agonist, while TLR4 knockout protects against anxiety-like behavior associated with ethanol withdrawal (Pascual et al., 2011). However, in the amygdala, other molecules, including monocyte chemoattractant protein-1 (MCP-1), nitric oxide synthase 2 (NOS-2) or tumor necrosis factor alpha (TNFα), were increased following withdrawal (Freeman et al., 2012). This region is also associated with elevated IL-1β after ethanol administration (Marshall et al., 2016), indicating that generalized inflammation takes

place in regions regulating affective behavior. Increased inflammation is also present in human studies, where pro-inflammatory cytokine levels in the plasma of patients with alcohol use disorder positively correlated with depression and anxiety symptoms during withdrawal (Leclercq et al., 2012). This underlines the fact that biological dysfunctions in this phase of the addiction cycle are highly overlapping with mechanisms of mood disorders, in particular depression.

5.3. *Preoccupation-Anticipation*

Inflammation is also reported to be increased during the preoccupation-anticipation phase, with few differences compared with previous phases. Here too, craving behavior and regions responsible for executive functions, including inhibitory control, have been associated with increased TLR4 signaling. In consequence, the levels of cyclooxygenase-2 (COX-2) and apoptosis are elevated in the frontal cortex, a region crucial in executive control, in models of chronic ethanol addiction (Alfonso-Loeches et al., 2010; Knapp and Crews, 1999). This behavior also negatively correlates with levels of several TLRs, as well as levels of HMGB1 in the PFC in experiments modelling behavioral flexibility, the ability change our behavior based on external changes (Crews et al., 2017; Vetreno and Crews, 2012). In patients, obsessional craving scores similarly negatively correlate with IL-1β and IL-8 expression in peripheral blood mononuclear cells (Leclercq et al., 2014). While large amount of evidence supports the prominent role of TLR receptors, particularly TLR4, in addiction, these do not seem to modulate specific behaviors. Instead, TLR4-sustained inflammation appears to be a general mechanism of addiction, indistinctly present through all the behavioral phases.

6. The role of the HPA axis

All aforementioned systems have a reciprocal relationship with the stress-processing system, mainly constituted by the HPA axis (Figure 1). Dysregulation of this system is known to underlie withdrawal-related negative affect and increased stress responsivity.

6.1. *Intoxication*

The HPA axis is readily involved during the first stage of addiction, that of intoxication. More precisely, the HPA axis is initially activated upon drug-taking and becomes dysregulated with repeated administration (Koob and Le Moal, 2008). Because it has effects in the extended amygdala, activation of the HPA axis drives anxiety-like states, but also transition to compulsive drug-seeking behaviors (Koob et al., 2014). In normal circumstances, HPA axis activation triggers corticotropin releasing factor (CRF) release in the hypothalamus, which is then negatively regulated through systemic release of the main stress hormones, glucocorticoids (Keller-Wood and Dallman, 1984). Most drugs of abuse activate the HPA axis in this manner, which was shown to facilitate drug reward, as well as acquisition of drug-seeking behavior (Fahlke et al., 1996; Piazza et al., 1993; Piazza and Le Moal, 1997), including the likelihood of drug self-administration (Maccari et al., 1991; Steckler and Holsboer, 2001). However, with repeated HPA axis activation, such as upon repeated alcohol exposure, the extrahypothalamic CRF system becomes sensitized. This further increases CRF and glucocorticoids release, and thus drug-seeking (Maccari et al., 1991; Shepard et al., 2000) Thus, creating a cycle where the HPA axis increasingly drives drug-seeking, starting with an initial activation upon acute drug consumption, and followed by hyperactivity and sensitization after long-term exposure.

6.2. *Withdrawal*

The HPA axis, a fundamental regulator of the biological stress response, plays a crucial role in the withdrawal phase and the ensuing increase in stress function. As mentioned in the previous section, glucocorticoid levels are elevated in consequence to repeated intoxication. This also seems to underlie withdrawal-induced anxiety, together with CRF release in the extended amygdala (Koob and Kreek, 2007). This dysphoric state creates a process of negative reinforcement, where the absence of the drug is associated with anxiety, and contributes to compulsive drug-seeking in an attempt to remove the negative experience of drug withdrawal (Koob and Schulkin, 2019). These negative emotions associated with withdrawal have been explained by excessive release of CRF and can, in fact, be reversed with CRF antagonists (Koob, 2015). This mechanism, together with excessive activation of the NAc, also leads to the release of stress neuropeptide dynorphin, a κ opioid receptor agonist. The recruitment of the κ-dynorphin system, in turn, decreases NAc DA release and thus, decreases the reward sensation (Spanagel et al., 1990). Therefore, following acute withdrawal, elevated reward thresholds are observed, which eventually results in a negative emotional state (Land et al., 2009; Schindler et al., 2010). Illustrating this, anxiety-like and reward deficits associated with withdrawal can be blocked by κ-opioid receptor antagonists (Chartoff et al., 2012). Overall, withdrawal is characterized by a hypoactivity of the reward system, caused by an increase in stress function through CRF and dynorphin, which ultimately drives negative affect and reinforcement (Koob et al., 2014; Koob and Schulkin, 2019).

6.3. *Preoccupation-Anticipation*

Following withdrawal, the HPA axis plays an important role in the preoccupation-anticipation stage, especially since stress may be responsible for up to two-thirds of relapse

occurrences (Larimer and Marlatt, 1992). Indeed, the lingering HPA axis sensitization drives vulnerability to relapse during protracted abstinence as well as compulsive drug-seeking seen in the preoccupation-anticipation stage (Koob and Le Moal, 2008). The sensitized stress system impairs the top-down inhibitory control of the PFC over the basal ganglia and the extended amygdala (Koob and Le Moal, 2001). These mediate impulsivity and compulsivity, which are associated with relapse, and are responsible for executive control over motivated behavior (Barreno et al., 2019; Dalley et al., 2011). Indeed, the residual glucocorticoid system activation during this stage contributes to vulnerability to stress-induced relapse, as higher levels of corticosterone may increase the salience of objects or cues associated with reward and drug administration (Piazza et al., 1993). As evidence, animals undergoing protracted abstinence from alcohol show an upregulation of glucocorticoid receptors (GRs) in the NAc and amygdala, and chronic GR antagonism prevents consequent escalations in compulsive alcohol intake (Vendruscolo et al., 2012, 2015). Overall, the previous studies indicate that sensitization and overactivation of the HPA axis contributes to impairments in executive control, possibly via glucocorticoid-mediated mechanisms, participating in enhanced susceptibility to addiction relapse.

7. Conclusion

Substance and alcohol use disorders are one of the biggest health problems facing society today, and current prevention therapies and treatment strategies for addiction have limited efficacy and application. Early research into addiction focused on the mechanisms of acute reward following drug exposure, leading to the discovery of a consequent dopamine release repeatedly confirmed. Advances in neuroscience today have shifted the focus of research from dopaminergic activity in intoxication, onto the neuroadaptations that occur across the three-phase cycle of

addiction. This investigation highlighted the involvement of several other systems. Neurotransmitter systems such as endocannabinoids have been shown to be engaged and have their neurotransmitter levels increased, leading to a dysregulation and consequent hypoactivity in subsequent stages of withdrawal and preoccupation-anticipation. The same type of direction of dysregulation, from initial activation to sensitization and diminished activity, is seen in the case of the stress system, previously thought to only be engaged during the withdrawal phase. In the case of the inflammatory system, a general heightened response is seen throughout the disorder. Research into these circuits has allowed for the identification of new targets for treatments. Here, we have highlighted receptors and transcription factors which may drive maladaptive neuroplasticity and maintenance of addiction. Additional gaps remain in the study of substance use disorders today. Although the majority of individuals suffering from addiction use more than one substance and often show comorbidities with other mental health disorders, this is often neglected in clinical studies. This could possibly be overcome by considering an overlap of systems affected both in substance use and other neuropsychiatric disorders. As addiction is a complex disorder affecting each individual differently, it is unlikely that a single mechanism may adequately explain every aspect of it. Therefore, future research should focus on the relationships between the neurobiological mechanisms aforementioned and their synergic contributions to the etiology of addiction.

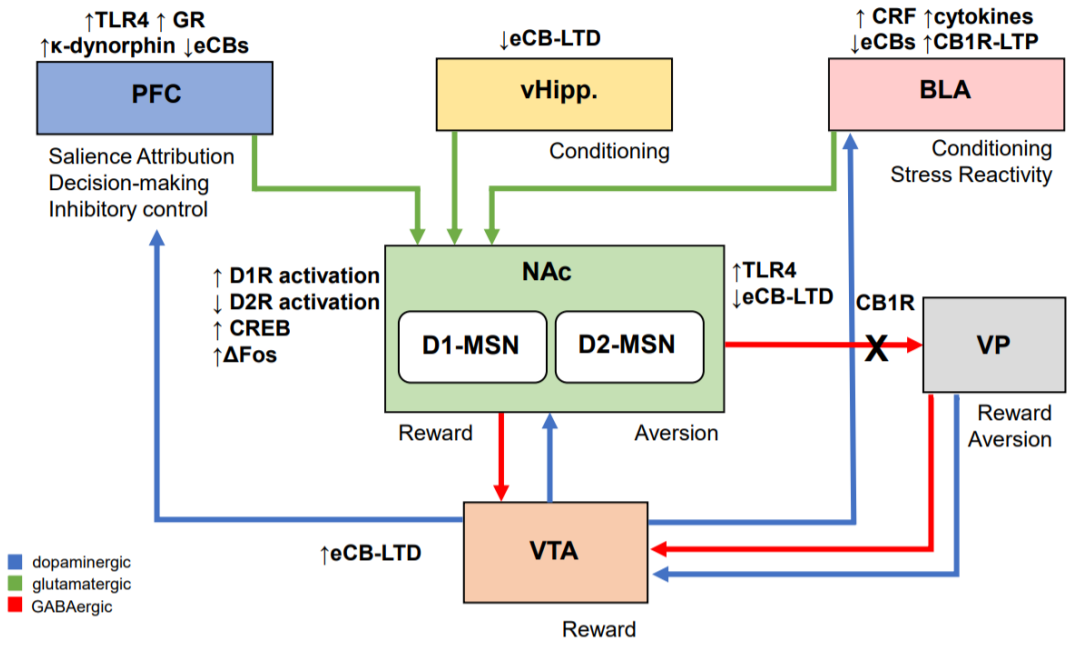

Figure 1. The Reward Circuit and Dysregulations of Neurotransmitter and Biological Systems Contributing to the Development of Addiction.

A rewarding stimulus, such as administration of drugs of abuse, selectively modulates excitatory input to VTA neurons that project to the NAc, leading to phasic firing and DA release. In the NAc, dopaminergic signals from the VTA are processed by GABAergic MSNs defined as D1R-expressing or D2R-expressing MSNs. D1-MSN stimulation increases the probability of action potential generation by excitatory inputs, resulting in preference, whereas D2R tonic stimulation has an inhibitory effect, encoding for aversion. The NAc also integrates information regarding internal state encoded by glutamatergic inputs from the limbic system including vHipp., PFC, and BLA. D1-MSN and D2-MSN activation may also activate or inhibit the VTA, respectively, via inhibitory projections to the VP.

Specific dysregulations pertaining to the endocannabinoid, immune and stress systems are included alongside the reward node regions. Main signaling and plastic mechanisms shown to be involved in the establishment and maintenance of addiction are highlighted.

Legend: Arrows indicate dopaminergic (blue), glutamatergic (green) and GABAergic (red) projections; crosses indicate inhibition. PFC: prefrontal cortex; vHipp.: ventral hippocampus; BLA: basolateral amygdala; NAc: nucleus accumbens; VP: ventral pallidum; VTA: ventral tegmental area; D1R: dopamine receptor type 1; D2R: dopamine receptor type 2; MSN: medium spiny neuron; D1-MSN: dopamine receptor type 1-expressing medium spiny neuron; D2-MSN: dopamine receptor type 2-expressing medium spiny neuron; CREB: cAMP response element-binding protein;. eCB: endocannabinoid; eCB-LTD: endocannabinoid-mediated long-term depression; CB1R: cannabinoid receptor type 1; CB1R-LTP: cannabinoid receptor type 1-dependent long-term potentiation; TLR4: toll-like receptor 4; CRF: corticotropin-releasing factor; GR: glucocorticoid receptors; ↑: increase; ↓: decrease.

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