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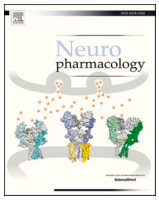

Neuronal adaptations in the lateral habenula during drug withdrawal: Preclinical evidence for addiction therapy

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ABSTRACT

The epithalamic lateral habenula (LHb) regulates monoaminergic systems and contributes to the expression of both appetitive and aversive behaviours. Over the past years, the LHb has emerged as a vulnerable brain structure in mental illnesses including addiction. Behavioural and functional evidence in humans and rodents provide substantial support for a role of LHb in the negative affective symptoms emerging during withdrawal from addictive substances. Multiple forms of cellular and synaptic adaptations that take hold during drug withdrawal within the LHb are causally linked with the emergence of negative affective symptoms. These results indicate that targeting drug withdrawal-driven adaptations in the LHb may represent a potential strategy to normalize drug-related behavioural adaptations. In the current review we describe the mechanisms leading to functional alterations in the LHb, as well as the existing interventions used to counteract addictive behaviours. Finally, closing this loop we discuss and propose new avenues to potentially target the LHb in humans in light of the mechanistic understanding stemming from pre-clinical studies. Altogether, we provide an overview on how to leverage cellular-level understanding to envision clinically-relevant approaches for the treatment of specific aspects in drug addiction.

1. Introduction

Drug addiction emerges when drug intake becomes repetitive and compulsive, despite the negative consequences this may entail (Koob and Le Moal, 2001). This mental disorder comprises recurring periods of drug intake, withdrawal, and relapse. The interruption of chronic drug intake, leading to absence of the drug from the system after a protracted period of abstinence, produces a negative state characterized by the emergence of depressive-like symptoms, hereafter termed withdrawal period (Barr et al., 2002; Everitt and Robbins, 2005). The experience of the withdrawal state is key in the development of addiction, but also difficult to approach from a clinical standpoint.

The withdrawal state includes physical and psychological symptoms such as distress and anhedonia, which can arise during withdrawal from psychostimulants, opiates, alcohol, tobacco or cannabis (West and Gossop, 1994; Koob and Le Moal, 2001). In light of this, drug withdrawal-induced mood disturbances were proposed as a potent driving force for relapse (Koob et al., 2014).

In this review we address the synaptic and cellular adaptations in rodents underlying aspects of drug withdrawal, and focus on the contribution of the epithalamic lateral habenula (LHb) to this process and highlight existing and potential interventions to ameliorate the human condition. Recent review articles describe in detail the neuronal circuit implicated in drug addiction or the modification drug withdrawal leads in the LHb. The original objective of this review is to bridge recent advances in circuit neuroscience with clinical aspects related to drug abuse. Rather than a systematic review of the literature, here we make an effort to merge distinct fields and make it accessible to a broad audience of fundamental scientists and clinicians.

The LHb has a pivotal role in reward and aversion processing and contributes to the negative affective aspects of neuropsychiatric disorders including depression and addiction (Hikosaka, 2010; Lecca et al., 2014). LHb neuronal hyperactivity emerges in depressed patients, and studies in humans, monkey and rodents indicate that LHb activity encodes punishments (Morris et al., 1999; Matsumoto and Hikosaka, 2009; Salas et al., 2010). These studies were seminal in promoting the idea that negative aspects of drug addiction, and especially withdrawal symptoms, may rely on adaptations at the level of the LHb. In combination with pre-clinical and clinical observations suggesting that LHb targeting ameliorates pathological conditions, we offer insights on how to design therapeutical strategies elaborating from mechanistic knowledge.

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Abbreviations

AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
CaMKII	calcium/calmodulin-dependent protein kinase II
DBS	deep brain stimulation
Dreadd	designer receptors exclusively activated by designer drug
DRN	dorsal raphe nucleus
EPN	entopeduncular nucleus
ERK	extracellular signal-regulated kinases
GABA	γ-aminobutyric acid
GLT	glutamate transporter
Kir	inwardly rectifying potassium
i.p	intraperitoneal
LHb	lateral habenula
mEPSC	miniature excitatory postsynaptic current
NAc	nucleus accumbens
NMDA	n-methyl-D- aspartate
RMTg	rostromedial tegmental nucleus
TMS	Transcranial magnetic stimulation
TNF	tumor necrosis factor
VS	ventral striatum
VTA	ventral tegmental area

2. Adaptations of the lateral habenula: a biomarker of drug withdrawal

An initial rationale that LHb can generally contribute to drug driven behaviours and plasticity lies in its connectivity. LHb neurons, which are mostly glutamatergic, target midbrain nuclei contributing to the reinforcing properties of drugs including the Ventral Tegmental Area (VTA) as well as the Rostromedial Tegmental Nucleus (RMTg) which in turn inhibits VTA dopamine neurons (Jhou et al., 2009; Omelchenko and Sesack, 2009; Beier et al., 2019; Nestler and Lüscher, 2019). In this review we will discuss the effects that withdrawal from psychostimulants, alcohol and morphine causes within the LHb. While few evidence related to other drugs exists (cannabinoids for instance) we decided to focus to the effects described by larger number of studies. Notably, continuous exposure to drugs of abuse including cocaine and amphetamines, followed by 2 days of withdrawal, induces degeneration of the fasciculus retroflexus, a dense fiber tract of LHb axons projecting to the midbrain (Carlson et al., 2000; Ellison, 2002). Furthermore, 14 days of withdrawal from a chronic heroin regimen (14 days self-administration) induces increases in c-fos reactivity – indicative of neural activity – within the LHb (Zhang et al., 2005). These early studies implicated the LHb's participation in the effects promoted by addictive drug exposure and, more specifically, in drug withdrawal thus providing the platform for more in-depth physiological investigation.

2.1. LHb activity and excitability in drug withdrawal

Withdrawal from both cocaine and ethanol elicit a pronounced increase in LHb neuronal activity and excitability. In rats, withdrawal following a 5-day cocaine self-administration protocol increases LHb neuron membrane excitability in acute slices correlating with an increase in membrane resistance (Neumann et al., 2014). This increase in excitability is present at 2 days and 7 days of withdrawal yet returns to baseline when measured at a later time point of 45 days. Similarly, membrane excitability and resistance increase in mice during 24 h withdrawal after two daily intraperitoneal (i.p.) injections of cocaine (Meye et al., 2015). Accordingly, LHb neuronal firing recorded in vivo is also elevated at this time point. Both the increased excitability and firing occur specifically in LHb neurons projecting to the RMTg. These adaptations are mediated by decreased potassium conductance, an inhibitory driving force key to regulating neuronal excitability (Meye et al., 2015).

A similar scenario emerges during ethanol withdrawal. Following a 24 h withdrawal period from chronic administration of ethanol in rats (i.p. and self-administration), LHb neurons exhibit both increased membrane excitability and in-vivo firing (Kang et al., 2017; Li et al., 2017). These cellular adaptations rely in part to a reduction in non-inactivating potassium current (M-type) potassium channel function, which was revealed by both a decrease in protein expression and diminished M-currents (Kang et al., 2017).

Thus, both cocaine and ethanol withdrawal drive an increase in LHb excitability which rely on decreased potassium conductance (Fig. 1). Whether the M current is the component affected in cocaine withdrawal, as it is in ethanol withdrawal, remains to be seen. In addition, alternative ion channels or scaffolding proteins could participate in this effect and it remains unknown whether this is the case, and if this process is similar for all classes of addictive substance.

2.2. Drug withdrawal-driven synaptic plasticity in LHb circuits

Complementing these reports of increased activity and excitability, synaptic plasticity in drug withdrawal largely, yet not exclusively, follows a pattern of strengthening excitatory synapses on to LHb and weakening inhibitory inputs.

Withdrawal from 5 daily i.p. cocaine injections produces a long lasting (present at 2 weeks of withdrawal) increase in amplitude of miniature excitatory post-synaptic potentials (mEPSCs), indicative of post-synaptic strengthening of glutamatergic transmission (Maroteaux and Mameli, 2012; Meye et al., 2015). Accordingly, the AMPA:NMDA ratio, a well-recognized proxy for post-synaptic strength, also increases after 24 h of withdrawal from 2 daily i.p. cocaine injections. Like the concomitant increase in activity, this plasticity occurs specifically in LHb neurons projecting to the RMTg (Meye et al., 2015). Drawing on the high expression of GluA1-containing AMPA receptors at LHb excitatory synapses, the authors investigated whether these post-synaptic modifications were a result of increased GluA1 trafficking to the cell membrane (Meye et al., 2013). Blocking the trafficking of GluA1 to the cell membrane in the LHb prevented the withdrawal-driven changes in mEPSCs and AMPA:NMDA. Interestingly, this intervention also prevented the reduction in potassium conductance and consequent hyperexcitability, suggesting these changes in excitability/activity may occur downstream of synaptic potentiation (Meye et al., 2015).

Similarly to cocaine, 24 h withdrawal from 8 weeks of chronic intermittent ethanol self-administration also induces an increase in AMPA:NMDA which occurs alongside elevated trafficking of GluA1 AMPA receptors (Li et al., 2017). Whilst both cocaine and ethanol withdrawal influence GluA1 delivery to the synaptic membrane, they recruit distinct mechanisms to reach this end. GluA1 trafficking is tightly regulated by the phosphorylation of different serine residues of the GluA1 C-Terminus (S845 and S831 for instance (Esteban et al., 2003)). In cocaine withdrawal, phosphorylation of S845, but not S831, increases and is critical for the resultant synaptic strengthening (Meye et al., 2015). In contrast, S831 phosphorylation increases in ethanol withdrawal while inhibiting Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) activity – which mediates S831 phosphorylation - prevents the resultant hyperexcitability (Li et al., 2017). This again illustrates the intertwined relationship of changes in synaptic plasticity and excitability in the LHb. Overall, both cocaine and ethanol withdrawal strengthen excitatory synapses in the LHb by recruiting GluA1 trafficking, which also influences withdrawal-driven hyperexcitability (Fig. 1).

Several studies have demonstrated that inhibitory transmission on to LHb neurons is diminished in aversive states (Lecca et al., 2016; Meye et al., 2016; Tchenio et al., 2017). A major input to the LHb arising from the Entopeduncular Nucleus (EPN) co-releases both GABA

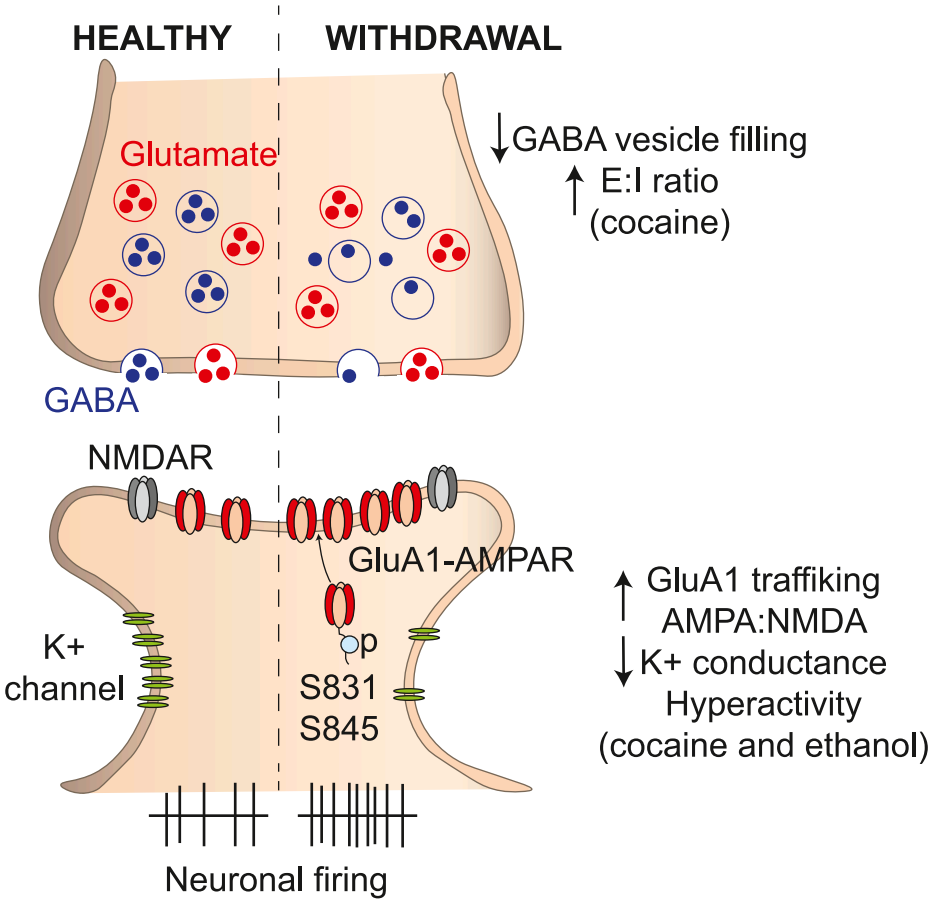

Fig. 1. Drug-driven adaptations within the LHb. Withdrawal from cocaine and ethanol drive common adaptations in LHb neurons. Cocaine and ethanol: Phosphorylation of GluA1-serine residues potentiates trafficking of AMPA receptors to the cell membrane, thus increasing the AMPA:NMDA ratio - strengthening excitatory synaptic transmission. Reductions in potassium conductance ultimately drive hyperactivity. Cocaine: Impaired presynaptic (from EPN) GABAergic vesicle filling drives an increase in E:I ratio at this input.

(γ-aminobutyric acid) and glutamate (Shabel et al., 2014). In cocaine withdrawal the ratio of these two opposing synaptic driving forces is shifted towards excitation at both 2 and 14 days of withdrawal following 5 daily i.p. injections (Shabel et al., 2014; Meye et al., 2016). This change in excitatory/inhibitory ratio (E:I ratio) is mediated by impaired GABAergic vesicle filling, resulting in diminished GABA release and a consequent decrease in $GABA_A$ receptor currents (Fig. 1). This plasticity seems specific to the EPN input, as similar cocaine withdrawal-driven changes in E:I ratio were absent when globally targeting all inputs to the LHb with electrical stimulation. Further experiments revealed that this same mechanism also accounts for a decrease in $GABA_B$ currents (Tan et al., 2019). Thus, synergistic excitatory postsynaptic and inhibitory presynaptic adaptations act in concert to amplify excitation of LHb neurons. Whether similar GABAergic plasticity in LHb occurs during withdrawal from other drugs is currently unknown.

These complementary adaptations in both excitatory and inhibitory transmission in the LHb during cocaine withdrawal, in tandem with increased excitability provide a cellular substrate for the increased activity during drug withdrawal of downstream structures including the RMTg (Jhou et al., 2013). The LHb sends direct projections as well to VTA neurons, however, cocaine withdrawal has not resulted in detectable adaptations at VTA projecting cells (Meye et al., 2015). It is plausible however, that the inability to distinguish LHb neurons controlling distinct VTA populations has masked potential divergent adaptations within the LHb. Accordingly, 14 days of cocaine withdrawal after 5 daily i.p. injections drives opposing effects on presynaptic release probability at distinct VTA subsets. LHb neurotransmitter release probability at medial prefrontal cortex (mPFC) projecting neurons increases during withdrawal, whereas it is diminished at nucleus accumbens (NAc) projectors, circuits shown to regulate aversion and reward respectively (Clerke et al., 2021; Lammel et al., 2012; Weele et al., 2019; Zell et al., 2020; Tam and Roth, 1985; Morrow et al., 1996). Future experiments should seek to utilize advancements in transgenic rodent lines and sophisticated viral tools to define the contributions of distinct pathways within this complex circuitry.

Whilst the literature described thus far describes complementary adaptations supporting greater excitation of LHb, this is not universal to all withdrawal contexts. Withdrawal from 6 daily i.p. morphine injections drives a decrease in AMPA:NMDA ratio in LHb neurons projecting to the Dorsal Raphe Nucleus (DRN (Valentinova et al., 2019)). This plasticity was observed in nalaxone-precipitated withdrawal where the mu-opioid antagonist is used to quickly induce the withdrawal state, as well as in spontaneous withdrawal up to 30 days following the last morphine injection. Furthermore, this is not the sole instance of decreased excitation in an aversive context. Recent work has demonstrated a decrease in AMPA:NMDA in the LHb after footshock stress, which mediates consequent behavioural maladaptations (Nuno-Perez et al., 2021). These results demonstrate a greater complexity and nuance that may depend on factors including the neuronal circuits in which the LHb population is embedded. Crucially in both these recent studies, as well as those reporting excitatory potentiation and inhibitory depression in the LHb, the adaptations were shown to be fundamental for the emergence of aversive states and maladaptive behaviours.

Overall, while cocaine and ethanol withdrawal-mediated effects in the LHb present similarities, this is not the case for opioid like morphine. It remains complex to state whether these effects are local within the LHb or emerging after a cascade of processes during the withdrawal period. The second scenario seem more plausible. If cocaine and ethanol engage similar circuit modification, these effects will converge onto changes in potassium conductance in the LHb to exert the similar effects described above. One interesting direction would be to test whether the cellular processing underlying opioid-driven adaptations also occur in

cocaine or ethanol withdrawal. Future studies will be necessary to clarify these aspects.

2.3. Involvement of glial systems in the LHb during withdrawal

Recent years have witnessed a greater appreciation throughout neuroscience fields of the importance of glia in shaping physiology and pathological disease states, including addiction to drugs of abuse (Lacagnina et al., 2017). Groundbreaking evidence support a critical role of astroglial potassium channels in regulating LHb neuronal burst firing (Cui et al., 2018; Yang et al., 2018). Upregulation of Kir 4.1 potassium channels enhances clearance of extracellular potassium, thus hyperpolarizing neuronal membrane potential and, as a result, increasing the proportion of rebound bursting neurons (Cui et al., 2018). Overall, this strengthens the involvement of LHb glia in regulating LHb neuronal activity.

In this context, recent work has shown that glial adaptations in LHb are key components responsible for shaping the hyperactivity in ethanol withdrawal and synaptic plasticity in morphine withdrawal. 24 h ethanol withdrawal following twice-daily i.p. injections for 10 days reduces LHb expression of Glutamate Transporter GLT-1, a glutamate transporter predominantly found in astrocytes (Kang et al., 2018). GLT-1 is critical for astrocytic uptake of glutamate from the synaptic cleft. Reductions in its activity thus result in greater glutamate concentrations available to act on post-synaptic receptors, leading to hyperactivity. Restoring LHb GLT-1 function with ceftriaxone normalized firing rates in Ethanol withdrawn rats, whereas the effect of pharmacologically inhibiting GLT-1 function to increase firing was occluded (Kang et al., 2018). Altogether these data show that ethanol withdrawal-driven LHb hyperactivity is also tightly regulated by glial adaptations.

In the case of opiates, naloxone-precipitated withdrawal from morphine (6 daily i.p. injections) produces a pronounced increase in levels of the pro-inflammatory cytokine Tumor Necrosis Factor-α (TNF-α) in the LHb whilst reducing local microglial volume (Valentinova et al., 2019). This increase in TNF-α is critical to the emergence of morphine withdrawal-driven plasticity. The decrease in AMPA:NMDA ratio at LHb neurons can be mimicked by exogenous TNF-α and is dependent on intact endogenous TNF-α signaling within the LHb (Valentinova et al., 2019). These results are in line with previous literature where reduced microglial arborization and TNF-α dependent internalization of AMPA receptors were observed in the nucleus accumbens (NAc) following 5 daily cocaine injections (Lewitus et al., 2016). These studies raise the possibility that elevations in inflammatory signals throughout the brain may represent a feature of drug withdrawal, a phenomenon recognized in many other psychiatric disorders such as depression and schizophrenia (Lee and Guiliani., 2019; Müller et al., 2015).

Overall, non-neuronal cells dysfunction can be central to understanding the aetiology of neuronal adaptations in many different disease states including drug withdrawal.

2.4. Adaptations in the LHb shape negative behavioural state in withdrawal

The hyperactivity as well as the synaptic adaptations in the LHb during drug withdrawal occur along with emergence of negative states reminiscent of those typical of depression (i.e. depressive-like symptoms; Barr et al., 2002; Shabel et al., 2014; Meye et al., 2015; Tchenio et al., 2017). Several studies investigated whether cellular adaptations are causal for such behavioural phenotypes.

Withdrawal from cocaine evokes depressive symptoms such as anhedonia, and behavioural despair (Hatzigiakoumis et al., 2011; Meye et al., 2015). These depressive-like states rely on the LHb hyperactivity, which follows adaptations in postsynaptic excitatory and presynaptic inhibitory transmission (Meye et al., 2015, 2016). Notably, the degree of behavioural despair in cocaine withdrawal shows correlation with the ability of stress to induce reinstatement of cocaine preference during withdrawal (Meye et al., 2016). This experimental paradigm supports the scenario in which the aversive state in withdrawal renders individuals more susceptible to stress, and thereby more vulnerable to drug intake relapse. Importantly, preventing AMPA receptor trafficking and reduction in presynaptic GABA function via overexpression of the vesicular GABA transporter normalized the behavioural phenotype mediated by drug withdrawal (Meye et al., 2015, 2016).

Similarly, depressive and anxiety-like symptoms in ethanol withdrawal are also related to LHb hyperactivity. Indeed, ethanol withdrawal-driven anhedonia and behavioural despair are concomitant to adaptations in excitatory transmission and glial glutamate buffering, upstream of hyperactivity (Li et al., 2017). Furthermore, restoring the function of M-type potassium channels in the LHb rescues withdrawal-driven anxiety-like behaviours. This is consequent to the normalization of drug-driven hyperactivity (Kang et al., 2017).

Morphine withdrawal drives negative emotional states including sociability deficits (Goeldner et al., 2011; Welsch et al., 2020). This phenotype was prevented when morphine withdrawal cellular changes in the LHb were limited by ablating the receptor sensing TNFα within LHb, further supporting the recruitment of local cytokine signalling (Valentinova et al., 2019).

Altogether, these studies demonstrate that distinct cellular adaptations in the LHb are fundamental to the emergence of drug-driven aversive state. Thus, the LHb may represent a promising target for treatment of withdrawal symptoms and reducing the likelihood of promoting relapse. This certainly leads to the question of whether or not this knowledge sets a ground for clinical applications. For this reason, the next session will discuss the state of the art interventional approaches nowadays employed for addiction treatment.

3. Therapeutic strategies for treating drug addiction

On the basis of the general heuristic model of addiction (Koob and Volkow, 2010), the most pragmatic way to treat and cure substance use disorder requires two steps: first, it is necessary to facilitate discontinuation of ongoing drug use by managing the acute physical withdrawal syndrome. Secondly, it is essential to provide sustained support to avoid the occurrence of relapse episodes during protracted withdrawal, which is more psychological in nature (Koob and Le Moal, 2001; Volkow, 2020). However, the existing clinical strategies are mostly effective on the first step while much more effort needs to be done in order to support individuals against relapse.

3.1. Addiction and therapeutics – brief overview

Animal and human studies have highlighted multiple brain structures underlying independent phases in what is defined as the addiction cycle (Koob and Volkow, 2010). For example, the VTA and ventral striatum (VS) underlie the binge/intoxication stage; extended amygdala and lateral habenula (LHb) defective adaptations underpin the withdrawal stage; finally, frontal cortices, dorsal striatum, basolateral amygdala and hippocampus are at the basis of the preoccupation/anticipation stage (Koob and Le Moal, 2001; Koob and Volkow, 2010).

The American Food and Drug Administration have approved only few medications that are specific for treating drug addiction and they are limited to opioid, alcohol, and tobacco use disorders (Klein, 2016). In general, pharmacological agents are used to manage acute withdrawal syndromes caused by the wearing off of the drug within the system and to prevent the occurrence of relapse to compulsive drug use (O'Brien and Gardner, 2005). Most medications are represented by agonists that are used as replacements for the abused drug and are taken daily to avoid withdrawal and repeated drug intake (Douaihy et al., 2013). Giving a detailed description of the canonical pharmacotherapies used

for treating drug addicts is out of the scope of this review, yet this review intend to provide a general framework of the interventional approaches from the perspective of drug-withdrawal.

3.2. Novel therapeutic strategies anchored on pre-clinical findings

The work carried out by the addiction field in the last two decades shed light on the precise brain nodes and circuits that mediate the variety of pathological behaviours present in substance use disorder (Lüscher and Janak, 2021; Welsch et al., 2020; Dong and Nestler, 2014; Salery et al., 2021).

These specific structures undergo well-defined drug-induced detrimental rearrangements on the synaptic, genetic, epigenetic, and structural level (Koob and Volkow, 2010; Nestler and Lüscher, 2019). The significant product of this progress is the emergence of a new vision regarding the procedure to follow for curing drug addiction: to revert neuronal alterations is necessary in order to treat specific aspects of the disorder (Lüthi and Lüscher, 2014). Preclinical evidence suggests that this is possible in animal models of drug addiction both in rodents and non-human primates (Lüscher, 2016). In line with the scope of this section, we will focus on advancements in reverting neuronal dysfunction during drug withdrawal, an approach that has been tested successfully against depressive-like symptoms (Verplaetse and McKee, 2017; Koob, 2021) but also to improve impulse control (Sofuoglu et al., 2013).

3.2.1. Improving impulsivity

One trait of addictive behaviours is the emergence of impulsivity, which contributes partly to the probability of relapse (Jentsch and Taylor, 1999; Goldstein and Volkow, 2011). Frontal and parietal cortices govern these cognitive functions, which are fundamental to individuals' ability to control their actions in response to drug cues (Sarter, 2006). Basic cognitive enhancers such as cholinesterase inhibitors, nicotinic agonists and monoamine transporter inhibitors have been proposed for the treatment of addictions even though clinical studies have produced contradictory results (Sofuoglu et al., 2013).

Reports of glutamatergic plasticity from prefrontal to limbic regions driving cue-induced relapse have inspired alternative strategies to ameliorate impulsivity in addiction by restoring balance to these glutamatergic projections (Kauer and Malenka, 2007). For example, stimulating the extra-synaptic metabotropic glutamate receptors via N-acetylcysteine or positive allosteric modulators decreased cocaine seeking in animal models (Moussawi et al., 2009; Loweth et al., 2014).

In line with the idea of restoring physiological functioning of specific structures and circuits, transcranial magnetic stimulation (TMS) and deep brain stimulation (DBS) represent innovative noteworthy approaches. These two strategies were originally developed for depression, obsessive-compulsive disorders and neurological disorders such as Parkinson disease. However, preclinical evidence of their ability to restore specific maladaptive plasticity in precise brain nodes pivotal for impulsivity and compulsivity such as the prefrontal cortices and the striatum has driven their clinical application in addiction.

TMS is a non-invasive method for interfering with neuronal function by delivering electric field pulses into the brain (Barker et al., 1985; Di Lazzaro et al., 2008). Although the mechanisms remains elusive, TMS stimulation protocols promote a net (which may be direct or indirect) activation of the brain tissue and also secondary activation of several structures connected to the primary activation site (Ilmoniemi et al., 1997) resulting in behavioural changes (Zangen and Hyodo, 2002). For instance, localized stimulation of PFC, either electrically or using genetically encoded light-activated ion channels (optogenetically), reduces cocaine intake in rats (Chen et al., 2008, 2013). These findings inspired a clinical study in which high-frequency repetitive TMS (rTMS) of the dorsolateral PFC reduced cocaine use and craving in patients with cocaine use disorder (Terraneo et al., 2016). Additional clinical studies, albeit preliminary, provide further support for the potential role of rTMS in cocaine, alcohol and nicotine addiction (Politi et al., 2008; Ceccanti et al., 2015; Addolorato et al., 2017).

Unlike TMS, DBS involves a surgical procedure in order to implant a stimulating electrode in specific brain structures for delivering electrical pulses. Initial testing for addiction treatment in the VS and insular cortex of humans provided encouraging results (Hassan et al., 2020). Importantly, preclinical research has inspired its refined use as a strategy to revert cocaine-induced synaptic plasticity. For instance, low-frequency optogenetic stimulation of the excitatory projections to the NAc is able to reverse cocaine-evoked plasticity and erase drug-adaptive behaviours in mice (Pascoli et al., 2011). Additionally, acute low-frequency DBS, in combination with selective blockade of dopamine D1 receptors, mimics optogenetic normalization of synaptic transmission leading to a long-lasting abolishment of behavioural sensitization (Creed et al., 2015). Despite the need to further test this strategy in more "naturalistic" addiction models such as self-administration and reinstatement, Creed and colleagues suggest how novel DBS protocols can emulate successful optogenetic approaches in animal models, providing strong basis to exploit this strategy in clinical trials (Creed et al., 2015).

3.2.2. Treating the drug-driven depressive-like symptoms

Another critical aspect that characterizes the withdrawal period is the emergence of a long phase dominated by depression-like symptoms such as dysphoria, anhedonia and anxiety, similar to those observed in animal models of depression, and all of which provide fertile ground for relapse (Koob and Le Moal, 2001; Koob and Volkow, 2010) (Barr et al., 2002). A significant negative emotional state is evident during withdrawal from drugs of abuse such as opioids and alcohol (Koob, 2021) as well as psychostimulants, tobacco, and cannabis (Barr et al., 2002; Koob, 2021).

Preclinical research has provided inspiration for novel strategies to treat addiction and multiple approaches have been explored in order to counteract the withdrawal negative state and to revert the neural maladaptations underlying these symptoms. For example, mifepristone, a glucocorticoid and progesterone receptor antagonist, blocked the escalation of drinking during withdrawal in rats and reduced alcohol consumption in humans (Vendruscolo et al., 2012, 2015). The reduction in glucocorticoid receptor function by mifepristone links withdrawal symptoms to HPA axis and central amygdala stress signaling dysfunction (Vendruscolo et al., 2015). Another drug that has been exploited for this purpose is gabapentin, normally used as an anticonvulsant and pain medication that has shown some promising effects in the treatment of alcohol use disorders (Leung et al., 2015). It is likely that gabapentin exerts its effect by decreasing GABAergic neurotransmission and therefore counteracting the GABAergic signaling dysfunction that contributes to drug taking (Dewey et al., 1998). For example, gabapentin decreased depressive-like symptoms in alcohol-dependent rats by reducing GABA inhibitory postsynaptic currents in the central amygdala (Roberto et al., 2008). This strategy has shown some encouraging results also in humans although with large individual variance (Laska et al., 2020). A recent study indicates that memantine, normally use as a medication in Alzheimer disease, might have beneficial effects on withdrawal-induced anxiety by suppressing the activation of the NMDA-CaMKII-ERK pathway in the mPFC and NAc shell (Yuanyuan et al., 2018). Ketamine, mostly employed as fast antidepressant, represents a promising strategy in the context of ethanol and heroin dependence, as well as in reducing self-administration of cocaine (Krupitsky et al., 2007; Sabino et al., 2013; Dakwar et al., 2019).

Altogether, intensive pharmacological and psychological treatment programs are the most widely used strategies. Emerging use of invasive (DBS) and non-invasive (TMS) approaches to functionally restore drug-driven maladaptations provides another avenue to target addiction. With the aim of providing new design and targets for treatment, the next chapter will discuss a line of interventions with a specific focus on the LHb.

4. LHb-tailored interventions to counteract addictive disorders

Findings from clinical and basic research converge to the idea that the LHb represents a major neural substrate for the depressive state emerging in both drug withdrawal and depression thereby highlighting its potential therapeutic relevance (Meye et al., 2017; Nuno-Perez et al., 2018). For instance, evidence that DBS of the LHb alleviates depressive symptoms in patients for whom multiple other interventions have failed has led to a greater appreciation of the importance of the LHb among clinicians and researchers alike (Sartorius et al., 2010; Wang et al., 2020). Whilst the research discussed above showcases the potential success that could be achieved from targeting LHb maladaptations to alleviate the negative state in withdrawal, this framework is yet to be translated into treatment in humans. Furthermore, how existing and prospective technologies could achieve this goal is currently unknown. This section intends to provide a reasoning on which approaches could enable targeting of the LHb for treatment of the withdrawal-driven negative state, helping to break the vicious cycle of drug addiction.

4.1. Mechanism-inspired use of DBS

A significant fraction of individuals affected by major depressive disorder, or obsessive-compulsive disorder do not find relief from standard pharmacological treatments. For those patients, DBS became a promising treatment option. DBS was approved for Parkinson's disease in 2002, and as of now its use is explored and implemented in a range of psychiatric disorders (Taghva et al., 2013). Despite the therapeutic success of DBS, its tailoring for specific disorders is hampered by the poor knowledge of the mechanisms underlying its effects (Vachez and Creed, 2020).

A corollary of this is the evidence that DBS within the habenula successfully ameliorated depressive symptoms in a patient where classic pharmacological treatment was not effective (Sartorius et al., 2010). This was the seminal evidence triggering a vast effort at the pre-clinical level to understand where and how DBS intervention was acting. This single-case study was the inspiration of initial work in rats whereby DBS in the LHb emulated the clinical findings. In a rodent model of depression - learned helplessness - the synaptic excitation onto LHb neurons, as well the neuronal activity of these cells was greater compared to control rats (Li et al., 2011). Using DBS within the LHb normalized the depressive-like state by reversing these functional adaptations, indicating an action at the local level (Li et al., 2011). In another study, early life stress produced depressive like symptoms in adulthood including defects in coping strategies as well as anhedonia (Tchenio et al., 2017). This occurred along with a decrease in the postsynaptic function of $GABA_B$ receptors, leading to an overall hyperexcitability of LHb neuronal populations. DBS within the LHb firstly reduced glutamate release, lowering synaptic excitation onto LHb neurons. Secondly, as a consequence of this intervention, it also reduced neuronal firing recorded in anesthetized animals producing a normalization of the depressive like state (Tchenio et al., 2017).

Can we leverage this knowledge around mood disorders for addictive behaviours? Using paradigms of sucrose and cocaine self-administration, rodents learn to make an effort in order to obtain the delivery of these rewards (Ahmed, 2010). DBS of LHb in rats reduced sucrose seeking and cocaine seeking behaviour in these self-administration paradigms (Friedman et al., 2010, 2011). Notably, DBS efficacy for this behaviour was prominent for a low dose of cocaine intake, rather than high doses (Lax et al., 2013), an effect due to the considerable neurodegeneration of the LHb-midbrain output pathway.

Several brain targets are suitable for DBS in the context of addiction, and this collection of research supports the LHb's inclusion within this network (Hassan et al., 2020). To better tailor the type of intervention however, a large effort is necessary to understand how DBS affects cellular and synaptic properties in the LHb. Future experiments will have however to determine the caveats around LHb stimulation. The connectivity of this structures to dopamine and serotonin centres needs consideration when designing potential interventions. In addition, more general effects on physiological behaviours will have to be assessed as LHb modulation may negatively affect feeding, sleep or emotional states (Stamatakis et al., 2016; Goutagny et al., 2013; Durieux et al., 2020). Overall, these new stream of research combined with the advancing knowledge in circuit neuroscience and optical stimulation approaches like optogenetics may inspire novel strategies to efficiently employ DBS in the human brain to ameliorate the negative state emerging in drug withdrawal (Creed et al., 2015).

4.2. Non-invasive strategies

A large effort of the last years produced alternative treatment approaches for substance use disorder, specifically, non-invasive brain stimulation. Importantly, this technology is using information on neuronal circuit interrogation to design appropriate therapeutic interventions (Ekhtiari and Paulus, 2016). Transcranial electrical stimulation and magnetic stimulation are non-invasive and at an early stage in their development for the treatment of addictive disorders. Although, a large number of structures have been targeted by these approaches, all of them are superficial cortical areas, as one caveat of the non-invasive methods is the lack of effectiveness onto deep brain structures (Ekhtiari et al., 2019). This prevents targeting deeper structures, like the LHb, and indicates that it may be used in combination with other approaches that can be either pharmacological or of other nature. An opening toward this is provided by the use of the fast antidepressant ketamine. Ketamine-assisted psychotherapy has been shown to significantly decrease relapse rates in heroin dependence (Krupitsky et al., 2007). Furthermore, the recent description that ketamine can normalize LHb hyperactivity to produce fast acting antidepressant effects (Yang et al., 2018) supports its use against the negative symptoms emerging during drug withdrawal. An effort at the pre-clinical and clinical level may allow better definition of the mechanisms underlying ketamine actions in addiction, and refine its use for therapeutically relevant interventions.

4.3. Genetic manipulation of LHb function

Chemogenetics allow the modulation of neuronal cells with cell type and region specificity through the viral-mediated expression of ligand-activated receptors (Lee et al., 2014).This neurotechnology permits the interrogation of neural circuits and unravel their contribution to animal behaviour. A genetic strategy is needed in this case to target the expression of the designer receptors exclusively activated by designer drugs (Dreadds) in specific neurons (Luchicchi et al., 2021). Through this mechanism, chemogenetics provides the ability to modulate neuronal firing for long periods with the single administration of a designer drug (Mondoloni et al., 2019; Walker and Kullmann, 2020).

A corollary stemming from such pre-clinical studies is that LHb neuronal activity is generally enhanced during cocaine withdrawal (Meye et al., 2015, 2016). A tentative prediction is that artificially reducing neuronal firing may represent a strategy to normalize the previously modified neuronal function and thus rescue associated symptoms. Chemogenetic inhibition of LHb neurons in rodents was successful in reducing their activity, an approach that ameliorated depressive like states in rodents (Tchenio et al., 2017; Coffey et al., 2020). The effectiveness of this strategy was successful in models of depression as well as rodent models of addiction. Notably, chemogenetic inhibition of LHb reduced reinstatement to cocaine after drug-self administration (Nair et al., 2021). Altogether, this provides evidence that chemogenetic approaches may represent a strategy for intervention to explore in humans.

Is this strategy a realistic approach suitable for the human condition?

The expression of these proteins within neuronal cells relies on the use of viral constructs as viable cargo. Despite the fact that viral tools engineered for experiments in rodents cannot be employed in humans,

gene therapy is nevertheless representing a viable alternative. Gene therapy is the introduction of transgenes into specific cells to treat disease. As of May 2019, there are more than 800 active investigational new drug applications for gene therapies (mostly Adeno Associated Virus-based) at the Food and Drug Administration (https://www.fda.gov/news-events/fda-voices-perspectives-fda-leadership-and-experts/fdas-efforts-advance-development-gene-therapy). When discussing gene therapy for application of chemogenetics in humans, several points of limitation need to be taken into consideration: *i.* how to deliver the chemogenetic receptor gene to only the targeted cell types, *ii.* how to achieve optimal expression of the chemogenetic receptor to generate a therapeutic effect with small molecule dosing and *iii.* enabling durable expression. Notably, the safety and side effects of the activator drug also need to be carefully determined. New exciting results show that this approach has potential for treating aspects of human diseases (Drew, 2018; Lieb et al., 2019). However, its applications for addictive disorders remains obscure, and no attempts have been made to determine whether this represents a viable strategy in the context of psychiatry.

5. Conclusions

Maladaptations taking place at the level of synapses, ion channel function and intracellular processes within the LHb represent neurobiological substrates contributing to the pathophysiology of drug addiction. More specifically, the majority of these changes mediate, at least partly, depressive-like symptoms among others contributing the negative state emerging during drug withdrawal, a powerful driver for relapse. The recent identification of molecular, cellular and synaptic players in the LHb underlying these negative states in animal models of both drug withdrawal and major depressive disorder now offers an opportunity to translate this knowledge into effective clinical treatments, thus helping to break the cycle of addiction.

CRediT authorship contribution statement

Joseph A. Clerke; Writing: Conceptualization, original draft preparation and final manuscript. Mauro Congiu; Conceptualization, original draft preparation and final manuscript. Manuel Mameli; Writing: Conceptualization, original draft preparation and final manuscript, Funding acquisition, Supervision.

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Declaration of competing interest

The authors have no conflicts of interest relevant to this article to disclose.

References

Addolorato, G., Antonelli, M., Cocciolillo, F., Vassallo, G.A., Tarli, C., Sestito, L., Mirijello, A., Ferrulli, A., Pizzuto, D.A., et al., 2017. Deep transcranial magnetic stimulation of the dorsolateral prefrontal cortex in alcohol use disorder patients: effects on dopamine transporter availability and alcohol intake. Eur. Neuropsychopharmacol 27 (5), 450–461.

Ahmed, S.H., 2010. Validation crisis in animal models of drug addiction: beyond non-disordered drug use toward drug addiction. Neurosci. Biobehav. Rev. 35 (2), 172–184.

Barker, A.T., Jalinous, R., Freeston, I.L., 1985. Non-invasive magnetic stimulation of human motor cortex. Lancet 1 (8437), 1106–1107.

Barr, A.M., Markou, A., Phillips, A.G., 2002. A 'crash' course on psychostimulant withdrawal as a model of depression. Trends Pharmacol. Sci. 23 (10), 475–482.

Beier, K.T., Gao, X.J., Xie, S., DeLoach, K.E., Malenka, R.C., Luo, L., 2019. Topological organization of ventral tegmental area connectivity revealed by viral-genetic dissection of input-output relations. Cell Rep. 26 (1), 159–167 e6.

Carlson, J., Armstrong, B., Switzer, R.C., Ellison, G., 2000. Selective neurotoxic effects of nicotine on axons in fasciculus retroflexus further support evidence that this a weak link in brain across multiple drugs of abuse. Neuropharmacology 39 (13), 2792–2798.

Ceccanti, M., Inghilleri, M., Attilia, M.L., Raccah, R., Fiore, M., Zangen, A., Ceccanti, M., 2015. Deep TMS on alcoholics: effects on cortisolemia and dopamine pathway modulation. A pilot study. Can. J. Physiol. Pharmacol. 93 (4), 283–290.

Chen, B.T., Bowers, M.S., Martin, M., Hopf, F.W., Guillory, A.M., Carelli, R.M., Chou, J. K., Bonci, A., 2008. Cocaine but not natural reward self-administration nor passive cocaine infusion produces persistent LTP in the VTA. Neuron 59 (2), 288–297.

Chen, B.T., Yau, H.J., Hatch, C., Kusumoto-Yoshida, I., Cho, S.L., Hopf, F.W., Bonci, A., 2013. Rescuing cocaine-induced prefrontal cortex hypoactivity prevents compulsive cocaine seeking. Nature 496 (7445), 359–362.

Clerke, J., Preston-Ferrer, P., Zouridis, I.S., Tissot, A., Batti, L., Voigt, F.F., Pagès, S., Burgalossi, A., Mameli, M., 2021. Output-specific adaptation of habenula-midbrain excitatory synapses during cocaine withdrawal. Front. Synaptic Neurosci. 13, 643138.

Coffey, K.R., Marx, R.G., Vo, E.K., Nair, S.G., Neumaier, J.F., 2020. Chemogenetic inhibition of lateral habenula projections to the dorsal raphe nucleus reduces passive coping and perseverative reward seeking in rats. Neuropsychopharmacology 45 (7), 1115–1124.

Creed, M., Pascoli, V.J., Lüscher, C., 2015. Addiction therapy. Refining deep brain stimulation to emulate optogenetic treatment of synaptic pathology. Science 347 (6222), 659–664.

Cui, Y., Yang, Y., Ni, Z., Dong, Y., Cai, G., Foncelle, A., Ma, S., Sang, K., Tang, S., et al., 2018. Astroglial Kir4.1 in the lateral habenula drives neuronal bursts in depression. Nature 554 (7692), 323–327.

Dakwar, E., Nunes, E.V., Hart, C.L., Foltin, R.W., Mathew, S.J., Carpenter, K.M., Choi, C. J.J., Basaraba, C.N., Pavlicova, M., et al., 2019. A single ketamine infusion combined with mindfulness-based behavioural modification to treat cocaine dependence: a randomized clinical trial. Am. J. Psychiatr. 176 (11), 923–930.

Dewey, S.L., Morgan, A.E., Ashby, C.R., Horan, B., Kushner, S.A., Logan, J., Volkow, N. D., Fowler, J.S., Gardner, E.L., et al., 1998. A novel strategy for the treatment of cocaine addiction. Synapse 30 (2), 119–129.

Di Lazzaro, V., Ziemann, U., Lemon, R.N., 2008. State of the art: physiology of transcranial motor cortex stimulation. Brain Stimul. 1 (4), 345–362.

Douaihy, A.B., Kelly, T.M., Sullivan, C., 2013. Medications for substance use disorders. Soc. Work. Publ. Health 28 (3–4), 264–278.

Dong, Y., Nestler, E.J., 2014. The neural rejuvenation hypothesis of cocaine addiction. Trends Pharmacol. Sci. 35 (8), 374–383.

Durieux, L., Mathis, V., Herbeaux, K., Muller, M.A., Barbelivien, A., Mathis, C., Schlichter, R., Hugel, S., Majchrzak, M., Lecourtier, L., 2020. Involvement of the lateral habenula in fear memory. Brain Struct. Funct. 225 (7), 2029–2044.

Drew, L., 2018. Gene therapy targets epilepsy. Nature 564 (7735). S10–S11.

Ekhtiari, H., Paulus, M., 2016. Preface: neuroscience for addiction medicine: from prevention to rehabilitation. Prog. Brain Res. 224 xxv–xxvi.

Ekhtiari, H., Tavakoli, H., Addolorato, G., Baeken, C., Bonci, A., Campanella, S., Castelo-Branco, L., Challet-Bouju, G., Clark, V.P., et al., 2019. Transcranial electrical and magnetic stimulation (tES and TMS) for addiction medicine: a consensus paper on the present state of the science and the road ahead. Neurosci. Biobehav. Rev. 104, 118–140.

Ellison, G., 2002. Neural degeneration following chronic stimulant abuse reveals a weak link in brain, fasciculus retroflexus, implying the loss of forebrain control circuitry. Eur. Neuropsychopharmacol 12 (4), 287–297.

Esteban, J.A., Shi, S.H., Wilson, C., Nuriya, M., Huganir, R.L., Malinow, R., 2003. PKA phosphorylation of AMPA receptor subunits controls synaptic trafficking underlying plasticity. Nat. Neurosci. 6 (2), 136–143.

Everitt, B.J., Robbins, T.W., 2005. Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. Nat. Neurosci. 8 (11), 1481–1489.

Friedman, A., Lax, E., Dikshtein, Y., Abraham, L., Flaumenhaft, Y., Sudai, E., Ben-Tzion, M., Ami-Ad, L., Yaka, R., et al., 2010. Electrical stimulation of the lateral habenula produces enduring inhibitory effect on cocaine seeking behaviour. Neuropharmacology 59 (6), 452–459.

Friedman, A., Lax, E., Dikshtein, Y., Abraham, L., Flaumenhaft, Y., Sudai, E., Ben-Tzion, M., Yadid, G., 2011. Electrical stimulation of the lateral habenula produces an inhibitory effect on sucrose self-administration. Neuropharmacology 60 (2–3), 381–387.

Goeldner, C., Lutz, P.E., Darcq, E., Halter, T., Clesse, D., Ouagazzal, A.M., Kieffer, B.L., 2011. Impaired emotional-like behaviour and serotonergic function during protracted abstinence from chronic morphine. Biol. Psychiatr. 69 (3), 236–244.

Goldstein, R.Z., Volkow, N.D., 2011. Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. Nat. Rev. Neurosci. 12 (11), 652–669, 20.

Goutagny, R., Loureiro, M., Jackson, J., Chaumont, J., Williams, S., Isope, P., Kelche, C., Cassel, J.C., Lecourtier, L., 2013. Interactions between the lateral habenula and the hippocampus: implication for spatial memory processes. Neuropsychopharmacology 38 (12), 2418–2426.

Hassan, O., Phan, S., Wiecks, N., Joaquin, C., Bondarenko, V., 2020. Outcomes of deep brain stimulation surgery for substance use disorder: a systematic review. Neurosurg. Rev. https://doi.org/10.1007/s10143-020-01415-y. Epub ahead of print. PMID: 33037538.

Hatzigiakoumis, D.S., Martinotti, G., Giannantonio, M.D., Janiri, L., 2011. Anhedonia and substance dependence: clinical correlates and treatment options. Front. Psychiatr. 2, 10.
Hikosaka, O., 2010. The habenula: from stress evasion to value-based decision-making. Nat. Rev. Neurosci. 11 (7), 503–513.
Ilmoniemi, R.J., Virtanen, J., Ruohonen, J., Karhu, J., Aronen, H.J., Näätänen, R., Katila, T., 1997. Neuronal responses to magnetic stimulation reveal cortical reactivity and connectivity. Neuroreport 8 (16), 3537–3540.
Jentsch, J.D., Taylor, J.R., 1999. Impulsivity resulting from frontostriatal dysfunction in drug abuse: implications for the control of behavior by reward-related stimuli. Psychopharmacology (Berlin) 146 (4), 373–390.
Jhou, T.C., Fields, H.L., Baxter, M.G., Saper, C.B., Holland, P.C., 2009. The rostromedial tegmental nucleus (RMTg), a GABAergic afferent to midbrain dopamine neurons, encodes aversive stimuli and inhibits motor responses. Neuron 61 (5), 786–800.
Jhou, T.C., Good, C.H., Rowley, C.S., Xu, S.P., Wang, H., Burnham, N.W., Hoffman, A.F., Lupica, C.R., Ikemoto, S., 2013. Cocaine drives aversive conditioning via delayed activation of dopamine-responsive habenular and midbrain pathways. J. Neurosci. 33 (17), 7501–7512.
Kang, S., Li, J., Bekker, A., Ye, J.H., 2018. Rescue of glutamate transport in the lateral habenula alleviates depression- and anxiety-like behaviours in ethanol-withdrawn rats. Neuropharmacology 129, 47–56.
Kang, S., Li, J., Zuo, W., Fu, R., Gregor, D., Krnjevic, K., Bekker, A., Ye, J.H., 2017. Ethanol withdrawal drives anxiety-related behaviours by reducing M-type potassium channel activity in the lateral habenula. Neuropsychopharmacology 42 (9), 1813–1824.
Kauer, J.A., Malenka, R.C., 2007. Synaptic plasticity and addiction. Nat. Rev. Neurosci. 8 (11), 844–858.
Klein, J.W., 2016. Pharmacotherapy for substance use disorders. Med. Clin. 100 (4), 891–910.
Koob, G.F., 2021. Drug addiction: hyperkatifeia/negative reinforcement as a framework for medications development. Pharmacol. Rev. 73 (1), 163–201.
Koob, G.F., Buck, C.L., Cohen, A., Edwards, S., Park, P.E., Schlosburg, J.E., Schmeichel, B., Vendruscolo, L.F., Wade, C.L., et al., 2014. Addiction as a stress surfeit disorder. Neuropharmacology 76 Pt B, 370–382.
Koob, G.F., Le Moal, M., 2001. Drug addiction, dysregulation of reward, and allostasis. Neuropsychopharmacology 24 (2), 97–129.
Koob, G.F., Volkow, N.D., 2010. Neurocircuitry of addiction. Neuropsychopharmacology 35 (1), 217–238.
Krupitsky, E.M., Burakov, A.M., Dunaevsky, I.V., Romanova, T.N., Slavina, T.Y., Grinenko, A.Y., 2007. Single versus repeated sessions of ketamine-assisted psychotherapy for people with heroin dependence. J. Psychoact. Drugs 39 (1), 13–19.
Lacagnina, M.J., Rivera, P.D., Bilbo Glial, S.D., 2017. Neuroimmune mechanisms as critical modulators of drug use and abuse. Neuropsychopharmacology 42 (1), 156–177.
Lammel, S., Lim, B.K., Ran, C., Huang, K.W., Betley, M.J., Tye, K.M., Deisseroth, K., Malenka, R.C., 2012. Input-specific control of reward and aversion in the ventral tegmental area. Nature 491 (7423), 212–217.
Laska, E.M., Siegel, C.E., Lin, Z., Bogenschutz, M., Marmar, C.R., 2020. Gabapentin enacarbil extended-release versus placebo: a likely responder reanalysis of a randomized clinical trial. Alcohol Clin. Exp. Res. 44 (9), 1875–1884.
Lax, E., Friedman, A., Croitoru, O., Sudai, E., Ben-Moshe, H., Redlus, L., Sasson, E., Blumenfeld-Katzir, T., Assaf, Y., et al., 2013. Neurodegeneration of lateral habenula efferent fibers after intermittent cocaine administration: implications for deep brain stimulation. Neuropharmacology 75, 246–254.
Lecca, S., Meye, F.J., Mameli, M., 2014. The lateral habenula in addiction and depression: an anatomical, synaptic and behavioural overview. Eur. J. Neurosci. 39 (7), 1170–1178.
Lecca, S., Pelosi, A., Tchenio, A., Moutkine, I., Lujan, R., Hervé, D., Mameli, M., 2016. Rescue of GABAB and GIRK function in the lateral habenula by protein phosphatase 2A inhibition ameliorates depression-like phenotypes in mice. Nat. Med. 22 (3), 254–261.
Lee, H.M., Giguere, P.M., Roth, B.L., 2014. DREADDs: novel tools for drug discovery and development. Drug Discov. Today 19 (4), 469–473.
Lee, C.H., Giuliani, F., 2019. The role of inflammation in depression and fatigue. Front. Immunol. 10, 1696.
Leung, J.G., Hall-Flavin, D., Nelson, S., Schmidt, K.A., Schak, K.M., 2015. The role of gabapentin in the management of alcohol withdrawal and dependence. Ann. Pharmacother. 49 (8), 897–906.
Lewitus, G.M., Konefal, S.C., Greenhalgh, A.D., Pribiag, H., Augereau, K., Stellwagen Microglial, D., 2016. TNF-α suppresses cocaine-induced plasticity and behavioural sensitization. Neuron 90 (3), 483–491.
Li, B., Piriz, J., Mirrione, M., Chung, C., Proulx, C.D., Schulz, D., Henn, F., Malinow, R., 2011. Synaptic potentiation onto habenula neurons in the learned helplessness model of depression. Nature 470 (7335), 535–539.
Li, J., Kang, S., Fu, R., Wu, L., Wu, W., Liu, H., Gregor, D., Zuo, W., Bekker, A., et al., 2017. Inhibition of AMPA receptor and CaMKII activity in the lateral habenula reduces depressive-like behaviour and alcohol intake in rats. Neuropharmacology 126, 108–120.
Lieb, A., Weston, M., Kullmann, D.M., 2019. Designer receptor technology for the treatment of epilepsy. EBioMedicine 43, 641–649.
Loweth, J.A., Scheyer, A.F., Milovanovic, M., LaCrosse, A.L., Flores-Barrera, E., Werner, C.T., Li, X., Ford, K.A., Le, T., Olive, M.F., Szumlinski, K.K., Tseng, K.Y., Wolf, M.E., 2014. Synaptic depression via mGluR1 positive allosteric modulation suppresses cue-induced cocaine craving. Nat. Neurosci. 17 (1), 73–80.
Luchicchi, A., Pattij, T., Viaña, J.N.M., de Kloet, S., Marchant, N., 2021. Tracing goes viral: viruses that introduce expression of fluorescent proteins in chemically-specific neurons. J. Neurosci. Methods 348, 109004.
Lüscher, C., 2016. The emergence of a circuit model for addiction. Annu. Rev. Neurosci. 39, 257–276.
Lüscher, C., Janak, P.H., 2021. Consolidating the circuit model for addiction. Annu. Rev. Neurosci. https://doi.org/10.1146/annurev-neuro-092920-123905. Epub ahead of print.
Lüthi, A., Lüscher, C., 2014. Pathological circuit function underlying addiction and anxiety disorders. Nat. Neurosci. 17 (12), 1635–1643.
Maroteaux, M., Mameli, M., 2012. Cocaine evokes projection-specific synaptic plasticity of lateral habenula neurons. J. Neurosci. 32 (36), 12641–12646.
Matsumoto, M., Hikosaka, O., 2009. Representation of negative motivational value in the primate lateral habenula. Nat. Neurosci. 12 (1), 77–84.
Meye, F.J., Lecca, S., Valentinova, K., Mameli, M., 2013. Synaptic and cellular profile of neurons in the lateral habenula. Front. Hum. Neurosci. 7, 860.
Meye, F.J., Soiza-Reilly, M., Smit, T., Diana, M.A., Schwarz, M.K., Mameli, M., 2016. Shifted pallidal co-release of GABA and glutamate in habenula drives cocaine withdrawal and relapse. Nat. Neurosci. 19 (8), 1019–1024.
Meye, F.J., Trusel, M., Soiza-Reilly, M., Mameli, M., 2017. Neural circuit adaptations during drug withdrawal - spotlight on the lateral habenula. Pharmacol. Biochem. Behav. 162, 87–93.
Meye, F.J., Valentinova, K., Lecca, S., Marion-Poll, L., Maroteaux, M.J., Musardo, S., Moutkine, I., Gardoni, F., Huganir, R.L., et al., 2015. Cocaine-evoked negative symptoms require AMPA receptor trafficking in the lateral habenula. Nat. Neurosci. 18 (3), 376–378.
Mondoloni, S., Durand-de Cuttoli, R., 2019. A. Mourot **cell-specific neuropharmacology**. Trends Pharmacol. Sci. 40 (9), 696–710.
Morris, J.S., Smith, K.A., Cowen, P.J., Friston, K.J., Dolan, R.J., 1999. Covariation of activity in habenula and dorsal raphé nuclei following tryptophan depletion. Neuroimage 10 (2), 163–172.
Morrow, B.A., Elsworth, J.D., Roth, R.H., 1996. Tyrosine enhances behavioral and mesocorticolimbic dopaminergic responses to aversive conditioning. Synapse 22 (2), 100–105.
Moussawi, K., Pacchioni, A., Moran, M., Olive, M.F., Gass, J.T., Lavin, A., Kalivas, P.W., 2009. N-Acetylcysteine reverses cocaine-induced metaplasticity. Nat. Neurosci. 12 (2), 182–189.
Müller, N., Weidinger, E., Leitner, B., Schwarz, M.J., 2015. The role of inflammation in schizophrenia. Front. Neurosci. 9 372.
Nair, S.G., Smirnov, D.S., Estabrook, M.M., Chisholm, A.D., Silva, P.R., Neumaier, J.F., 2021. Effect of chemogenetic inhibition of lateral habenula neuronal activity on cocaine- and food-seeking behaviours in the rat. Addiction Biol. 26 (1) e12865.
Nestler, E.J., Lüscher, C., 2019. The molecular basis of drug addiction: linking epigenetic to synaptic and circuit mechanisms. Neuron 102 (1), 48–59.
Neumann, P.A., Ishikawa, M., Otaka, M., Huang, Y.H., Schlüter, O.M., Dong, Y., 2014. Increased excitability of lateral habenula neurons in adolescent rats following cocaine self-administration. Int. J. Neuropsychopharmacol. 18 (6).
Nuno-Perez, A., Tchenio, A., Mameli, M., Lecca, S., 2018. Lateral habenula gone awry in depression: bridging cellular adaptations with therapeutics. Front. Neurosci. 12, 485.
Nuno-Perez, A., Trusel, M., Lalive, A.L., Congiu, M., Gastaldo, D., Tchenio, A., Lecca, S., Soiza-Reilly, M., Bagni, C., et al., 2021. Stress undermines reward-guided cognitive performance through synaptic depression in the lateral habenula. Neuron.
O'Brien, C.P., Gardner, E.L., 2005. Critical assessment of how to study addiction and its treatment: human and non-human animal models. Pharmacol. Ther. 108 (1), 18–58.
Omelchenko, N., Sesack, S.R., 2009. Ultrastructural analysis of local collaterals of rat ventral tegmental area neurons: GABA phenotype and synapses onto dopamine and GABA cells. Synapse 63 (10), 895–906.
Pascoli, V., Turiault, M., Lüscher, C., 2011. Reversal of cocaine-evoked synaptic potentiation resets drug-induced adaptive behaviour. Nature 481 (7379), 71–75.
Politi, E., Fauci, E., Santoro, A., Smeraldi, E., 2008. Daily sessions of transcranial magnetic stimulation to the left prefrontal cortex gradually reduce cocaine craving. Am. J. Addict. 17 (4), 345–346.
Roberto, M., Gilpin, N.W., O'Dell, L.E., Cruz, M.T., Morse, A.C., Siggins, G.R., Koob, G.F., 2008. Cellular and behavioural interactions of gabapentin with alcohol dependence. J. Neurosci. 28 (22), 5762–5771.
Sabino, V., Narayan, A.R., Zeric, T., Steardo, L., Cottone, P., 2013. mTOR activation is required for the anti-alcohol effect of ketamine, but not memantine, in alcohol-preferring rats. Behav. Brain Res. 247, 9–16.
Salas, R., Baldwin, P., de Biasi, M., Montague, P.R., 2010. BOLD responses to negative reward prediction errors in human habenula. Front. Hum. Neurosci. 4, 36.
Salery, M., Godino, A., Nestler, E.J., 2021. Drug-activated cells: from immediate early genes to neuronal ensembles in addiction. Adv. Pharmacol. 90, 173–216.
Sarter, M., 2006. Preclinical research into cognition enhancers. Trends Pharmacol. Sci. 27 (11), 602–608.
Sartorius, A., Kiening, K.L., Kirsch, P., von Gall, C.C., Haberkorn, U., Unterberg, A.W., Henn, F.A., Meyer-Lindenberg, A., 2010. Remission of major depression under deep brain stimulation of the lateral habenula in a therapy-refractory patient. Biol. Psychiatr. 67 (2), e9–e11.
Shabel, S.J., Proulx, C.D., Piriz, J., Malinow Mood regulation, R., 2014. GABA/glutamate co-release controls habenula output and is modified by antidepressant treatment. Science 345 (6203), 1494–1498.
Sofuoglu, M., DeVito, E.E., Waters, A.J., Carroll, K.M., 2013. Cognitive enhancement as a treatment for drug addictions. Neuropharmacology 64, 452–463.
Stamatakis, A.M., Van Swieten, M., Basiri, M.L., Blair, G.A., Kantak, P., Stuber, G.D., 2016. Lateral hypothalamic area glutamatergic neurons and their projections to the lateral habenula regulate feeding and reward. J. Neurosci. 13;36 (2), 302–311.

Taghva, A.S., Malone, D.A., Rezai, A.R., 2013. Deep brain stimulation for treatment-resistant depression. World Neurosurg. 80 (3–4). S27.e17–24.
Tam, S.Y., Roth, R.H., 1985. Selective increase in dopamine metabolism in the prefrontal cortex by the anxiogenic beta-carboline FG 7142, 1 Biochem. Pharmacol. 34 (9), 1595–1598.
Tan, D., Nuno-Perez, A., Mameli, M., Meye, F.J., 2019. Cocaine withdrawal reduces GABA. Eur. J. Neurosci. 50 (3), 2124–2133.
Tchenio, A., Lecca, S., Valentinova, K., Mameli, M., 2017. Limiting habenular hyperactivity ameliorates maternal separation-driven depressive-like symptoms. Nat. Commun. 8 (1), 1135.
Terraneo, A., Leggio, L., Saladini, M., Ermani, M., Bonci, A., Gallimberti, L., 2016. Transcranial magnetic stimulation of dorsolateral prefrontal cortex reduces cocaine use: a pilot study. Eur. Neuropsychopharmacol 26 (1), 37–44.
Vachez, Y.M., Creed, M.C., 2020. Deep brain stimulation of the subthalamic nucleus modulates reward-related behaviour: a systematic review. Front. Hum. Neurosci. 14, 578564.
Valentinova, K., Tchenio, A., Trusel, M., Clerke, J.A., Lalive, A.L., Tzanoulinou, S., Matera, A., Moutkine, I., Maroteaux, L., et al., 2019. Morphine withdrawal recruits lateral habenula cytokine signaling to reduce synaptic excitation and sociability. Nat. Neurosci. 22 (7), 1053–1056.
Vendruscolo, L.F., Barbier, E., Schlosburg, J.E., Misra, K.K., Whitfield, T.W., Logrip, M.L., Rivier, C., Repunte-Canonigo, V., Zorrilla, E.P., et al., 2012. Corticosteroid-dependent plasticity mediates compulsive alcohol drinking in rats. J. Neurosci. 32 (22), 7563–7571.
Vendruscolo, L.F., Estey, D., Goodell, V., Macshane, L.G., Logrip, M.L., Schlosburg, J.E., McGinn, M.A., Zamora-Martinez, E.R., Belanoff, J.K., et al., 2015. Glucocorticoid receptor antagonism decreases alcohol seeking in alcohol-dependent individuals. J. Clin. Invest. 125 (8), 3193–3197.
Verplaetse, T.L., McKee, S.A., 2017. Targeting Stress Neuroadaptations for Addiction Treatment: a Commentary on Kaye et al. J. Stud. Alcohol Drugs 78 (3), 372–374.
Volkow, N.D., 2020. Stigma and the toll of addiction. N. Engl. J. Med. 382 (14), 1289–1290.
Walker, M.C., Kullmann, D.M., 2020. Optogenetic and chemogenetic therapies for epilepsy. Neuropharmacology 168, 107751.
Wang, Z., Cai, X., Qiu, R., Yao, C., Tian, Y., Gong, C., Zhang, Y., Xu, B., Zhang, D., et al., 2020. Case report: lateral habenula deep brain stimulation for treatment-resistant depression. Front. Psychiatr. 11, 616501.
Weele, C.M.V., Siciliano, C.A., Tye, K.M., 2019. Dopamine tunes prefrontal outputs to orchestrate aversive processing. Brain Res. 1713, 16–31.
Welsch, L., Bailly, J., Darcq, E., Kieffer, B.L., 2020. The negative affect of protracted opioid abstinence: progress and perspectives from rodent models, 1 Biol. Psychiatr. 87 (1), 54–63.
West, R., Gossop, M., 1994. Overview: a comparison of withdrawal symptoms from different drug classes. Addiction 89 (11), 1483–1489.
Yang, Y., Cui, Y., Sang, K., Dong, Y., Ni, Z., Ma, S., Hu, H., 2018. Ketamine blocks bursting in the lateral habenula to rapidly relieve depression. Nature 554 (7692), 317–322.
Yuanyuan, J., Junyan, Z., Cuola, D., Jingjing, C., Yuhui, S., Dan, X., Wei, D., Yongsheng, Z., 2018. Memantine attenuated alcohol withdrawal-induced anxiety-like behaviours through down-regulating NR1-CaMKII-ERK signaling pathway. Neurosci. Lett. 686, 133–139.
Zangen, A., Hyodo, K., 2002. Transcranial magnetic stimulation induces increases in extracellular levels of dopamine and glutamate in the nucleus accumbens. Neuroreport 13 (18), 2401–2405.
Zell, V., Steinkellner, T., Hollon, N.G., Warlow, S.M., Souter, E., Faget, L., Hunker, A.C., Jin, X., Zweifel, L.S., et al., 2020. VTA glutamate neuron activity drives positive reinforcement absent dopamine Co-release. Neuron 107 (5), 864–873 e4.
Zhang, F., Zhou, W., Liu, H., Zhu, H., Tang, S., Lai, M., Yang, G., 2005. Increased c-Fos expression in the medial part of the lateral habenula during cue-evoked heroin-seeking in rats. Neurosci. Lett. 386 (2), 133–137.