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Neural Plasticity in the Ventral Tegmental Area, Aversive Motivation during Drug Withdrawal and Hallucinogenic Therapy

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ABSTRACT

Aberrant glutamatergic signaling has been closely related to several pathologies of the central nervous system. Glutamatergic activity can induce an increase in neural plasticity mediated by brain-derived neurotrophic factor (BDNF) in the ventral tegmental area (VTA), a nodal point in the mesolimbic dopamine system. Recent studies have related BDNF dependent plasticity in the VTA with the modulation of aversive motivation to deal with noxious environmental stimuli. The disarray of these learning mechanisms would produce an abnormal augmentation in the representation of the emotional information related to aversion, sometimes even in the absence of external environmental trigger, inducing pathologies linked to mood disorders such as depression and drug addiction. Recent studies point out that serotonin (5-hydroxytryptamine, 5-HT) receptors, especially the 2a (5-HT2a) subtype, play an important role in BDNF-related neural plasticity in the VTA. It has been observed that a single administration of a 5HT2a agonist can both revert an animal to a nondependent state from a drug-dependent state (produced by the chronic administration of a substance of abuse). The 5HT2a agonist also reverted the BDNF-induced neural plasticity in the VTA, suggesting that the administration of 5-HT2a agonists could be used as effective therapeutic agents to treat drug addiction. These findings could explain the neurobiological correlate of the therapeutic use of 5HT2a agonists, which can be found in animals, plants and fungi during traditional medicine ceremonies and rituals to treat mood related disorders.

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Introduction

Aversive motivation is the capacity to avoid potentially noxious, punishing, or life threatening stimulus (Campese et al. 2015). In recent years, the hypothesis has been emerging that exacerbated aversive motivation, such as anxiety and/or depression, constitutes a key configuration that contributes to the initial inclination and compulsion of a subject to use substances of abuse for negative reinforcement (Flores Mosri 2019; Koob et al., 2016).

Beyond the monoamine theory, which states that mood related disorders are caused by a functional deficiency of biogenic amines at critical synapses in the brain (Barchas & Altemus, 1999; Heninger, Delgado, and Charney 1996), a new theory proposing that a disorder in the ability of the nervous system to adapt and respond to the environment (including neurogenesis, neuronal remodeling, and synapse formation) is involved in the pathological process of exacerbated aversive motivation (Cai, Huang, and Hao 2015). Changes in cortical and hippocampal plasticity have been associated to the expression of chronic aversive state in both humans and in animal models; where the neurotrophin Brain-derived neurotrophic factor (BDNF) plays a key role in regulating synapses and neurogenesis (Cai, Huang, and Hao 2015; Kimpton 2012). A BDNF decrease has been related to a reduction in cell volume, changes in glutamate receptors and in glial cells, in the hippocampus and the prefrontal cortex; linked to aversive motivation (Cai, Huang, and Hao 2015; Kimpton 2012). However, increased levels of BDNF have been associated with multiple pathologies where inflammation occurs, as in neuropathic pain (Coull et al. 2005), epilepsy (Binder et al. 2001), and the exacerbated plasticity, in the mesolimbic system, which occurs in aversive motivation linked to drug dependency. Consequently a therapy based on systemic or nonselective increments of BDNF might not be as effective (specific to drug motivation) as hypothesized, and may produce opposite effects than expected (Goves, 2007). Therefore, in order to effectively treat pathological aversive motivation, it would be necessary to find a pharmacological agent with high specificity, which should be able to both, decrease BDNF levels in the mesolimbic system and, at the same time, increase levels of BDNF in hippocampus and frontal cortex.

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The so-called classical hallucinogens (5-HT2a agonists) such as Psilocybin, Dimethyltryptamine (DMT), Bufotenin, LSD-25 and Mescaline have an ancient history of medical use (Carhart-Harris and Goodwin 2017; Johnson et al. 2019). In recent years, there has been increasing interest of people seeking to use these substances to treat mood-related disorders (dos Santos et al., 2016; Johnson & Griffiths, 2017; Johnson et al. 2019, 2019; Mithoefer, Grob, and Brewerton 2016; Muttoni, 2019; Nichols, Johnson, and Nichols 2017; dos Santos et al., 2019; Vargas-Perez and Doblin 2013). Experimental studies and preclinical evidence suggest that classical hallucinogens, administered in a supportive environment with preparatory and integrative mental care, can be used safely to treat a range of psychiatric conditions related to aversive motivation, such as end-of-life anxiety, drug addiction, obsessive-compulsive disorder and depression (DiVito and Leger 2020; Dos Santos Rg et al. 2016; Johnson, Garcia-Romeu, and Griffiths 2017; Johnson et al. 2019; Mithoefer, Grob, and Brewerton 2016; Muttoni, Ardissino, and John 2019; Nichols, Johnson, and Nichols 2017; RG et al. 2019; Vargas-Perez and Doblin 2013). Moreover, recent experimental evidence suggest that classical hallucinogens could be acting as a pharmacological agent with high specificity to effectively treat aversive motivation, promoting neural plasticity in the frontal cortex and hippocampus, and reducing BDNF-related increased plasticity in the mesolimbic system. For example, intraperitoneal administration of psilocybin increase neural plasticity in the hippocampus (Catlow et al. 2013) and frontal cortical pyramidal neurons (Raval et al. 2021; Shao et al. 2021), and enhances the extinction of aversive motivation related to fear conditioning in rodents. These results are aligned with the finding that psychedelic compounds such as LSD and DMT, among other, are able to increase dendritic arbor complexity, promote dendritic spine growth, and stimulate synapse formation on pyramidal neurons, both in vitro and in vivo. In the ventral tegmental area, the administration of psilacetin, a pro-drug of psilocin (Nichols et al., 1999) reverses the plastic changes in the mesolimbic system induced by BDNF-related aversive drug withdrawal symptoms (Vargas-Perez et al. 2017). It also has been observed that repeated self administrations of LSD attenuates the depressant effects of the kappa opioid receptor agonist U69,593 on intra cranial self-stimulation in the medial forebrain bundle in rodents (Sakloth, 2019).

Evidence points to negative reinforcement as being the motivationally prepotent element of the withdrawal syndrome (Baker et al. 2004). Numerous observations accord with the notion that the motivational basis of addictive drug use is the reduction or avoidance of aversive internal states associate to withdrawal from drug of abuse (Baker et al. 2004). The aim of this text is to describe the neurobiological framework underlying aversive motivation correlated with drug dependence and withdrawal. Particularly, how BDNF-related increased plasticity in the mesolimbic system, mainly in the VTA, plays an important role in the activation of aversive motivation related to withdrawal from a high impact hedonic stimulus. It has been observed that chronic drug administration activates BDNF-related neuronal plasticity in the VTA, which is necessary for both the establishment of an opiate-dependent state and aversive withdrawal motivation (Vargas-Perez et al. 2014). When rats are drug-dependent and in withdrawal, BDNF is able to produce a change in the function of the VTA receptors for gamma-aminobutyric acid type A (GABA-A) located on GABA neurons from its baseline, changing inhibitory effect on neuronal function to excitatory (Vargas-Perez et al., 2009). This punctual change promotes a shift from a drug-naïve (dopamine-independent system, which involves the brainstem tegmental pedunculopontine nucleus, TPP) to a drug-dependent state (dopamine-dependent reward system) (Vargas-Perez, Ting-A-Kee, and van der Kooy 2009a). The text also addresses the mechanisms of the neurobiological correlate of the therapeutic use of 5HT2a agonists in both reversing and preventing substance abuse disorder associated with BDNF-related exacerbated plasticity in the VTA during drug withdrawal. 5HT2a agonist can revert an animal to a non-dependent state from a drug dependent state by decreasing BDNF-induced neural plasticity in the VTA. Thus, 5HT2a agonists are able to revert an immature-like state in VTA GABAergic neurons caused by withdrawal from drugs of abuse. These effects are envisioned to be beyond the capacity of 5HT2a agonists to construct mystical experience, produce increments in cortical and hippocampal plasticity, and modulate the default mode network, and their associated therapeutic influences (DiVito and Leger 2020; Johnson et al. 2019)(Figure 1)

The opponent process theory of motivation

Negative reinforcement is a powerful motivational influence on drug use, and the escape or avoidance of a negative motivational state is a main reason for the use of addictive drugs (Baker et al. 2004). According to the opponent process theory, the withdrawal from a rewarding stimulus could become the main trigger for an aversive motivational state. The severity and duration of the aversive state depends largely on the

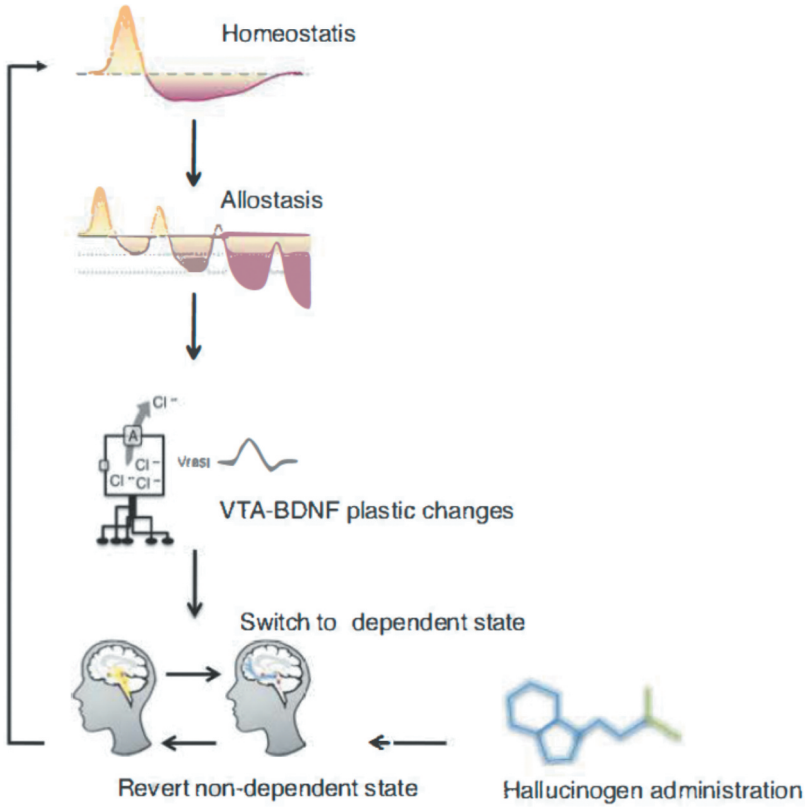

Figure 1. Summary figure. The administration of most drugs of abuse can produce a rewarding state and then, once the drug is eliminated from the organism, a withdrawal state emerges. Withdrawal from all major drugs of abuse produces the emergence of a negative emotional state as a consequence of a homeostatic control mechanism. The ingestion of a drug to avoid this aversive motivational state would produce a loop of withdrawal and drug intake. The negative state of drug withdrawal produces an increase in BDNF in the VTA. BDNF-related neuronal plasticity in the VTA is necessary for both the establishment of an opiate-dependent state and aversive withdrawal motivation. The administration of hallucinogens is able to block both the aversive conditioned response to drug withdrawal and the mechanism responsible for switching from a drug-naive to a drug-dependent motivational system.

intensity of the hedonic impact of the missing gratifying stimulus (Frenois, Le Moine, and Cador 2005; Solomon and Corbit 1974).

The opponent theory suggests that each time an organism is exposed to a stimulus, a series of changes occur to counteract the effects that the stimulus provokes in an effort to maintain the system in a basal state of dynamic equilibrium, or homeostasis (Solomon and Corbit 1974). An example of this occurs in the eye, with so-called ghost images or after-images: If an object of a certain color is held in central vision for an extended period of time, and then the observer closes their eyes or turns their eyes toward a neutral surface, they will see the negative after-image of the object without it being present (Solomon and Corbit 1974). In the case of emotions, a similar effect is thought to occur. In general, the presence of a stimulus produces a reaction (a-process), which is counteracted by a b-process to keep the system at its optimum limits (Solomon and Corbit 1974). The a-process has a rapid onset and similar duration to the stimulus that evokes it. When the stimulus is no longer present, the changes produced by the system to counteract the primary response produce the appearance of a second reaction (b-process), which is opposite in direction to the initial response, slower to initiate and longer lasting than the stimulus. An illustrative example could be the relationship of lovers, where the presence of the couple at first provokes a series of emotional reactions, normally of elation (a-process), but with the passage and sometimes almost imperceptibly, the system counteracts the primary response). However, if the rupture of the relationship or the sudden loss of one of the members occurs, then an opposite emotional reaction will be induced, most often a feeling of despondency (b-process) (Vargas-Perez, Ting-A-Kee, and van der Kooy 2009a) (Figure 2).

The emotional response to the administration of a drug of abuse follows the course established by the theory of the opponent processes (Vargas-Perez, Ting-A-Kee, and van der Kooy 2009a), When the

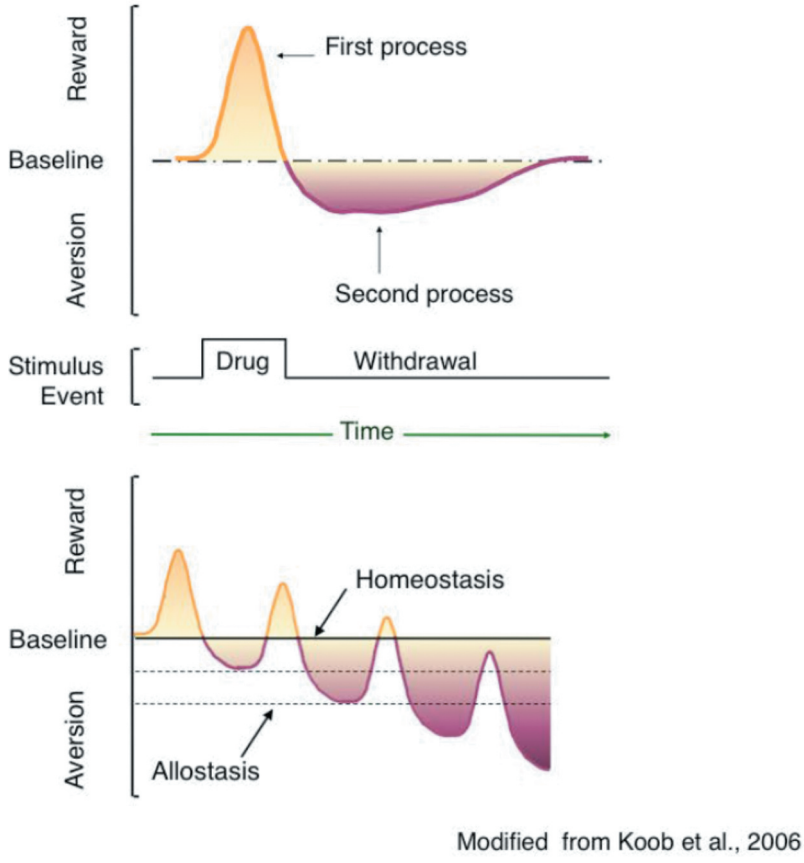

Figure 2. A. The opponent-process model for drug motivation in non-dependent animals. Drug intake arouses a positive first process (reward) that in turn elicits a negative aversive second 'opponent process' (aversion). B. Changes in motivational baseline after continuous drug intake. The aversive response will regularly lead to a new dose of the drug being ingested to counteract the unpleasant second process effects of abstinence, however, this generates a new, lower starting point for the opponent-process effects. When the baseline loses its initial stability and becomes a descendant cycle, it would lend to produce a state of lasting dysphoria,

drug (the stimulus) enters the body, it produces a feeling of euphoria (the a-process), followed by a period of stabilization while the substance is present. When the drug leaves the body and during withdrawal, an unpleasant reaction occurs (Vargas-Perez, Ting-A-Kee, and van der Kooy 2009a) (the opponent motivational b-process). This aversive response will regularly lead to a new dose of the drug being ingested to counteract the unpleasant b-process effects of abstinence through negative reinforcement. However this generates a new, lower starting point for the opponent process effects, which has as a consequence a decrease in the hedonic response produced by the same amount of drug, followed by a period of abstinence where the aversion is greater than the previous starting point. If this dynamic continues, individuals will require higher and higher doses of drugs to reverse the negative effects of abstinence, which are sometimes sufficient to reach only the original baseline level of comfort, without the experience of a period of euphoria (Koob et al. 1997) (Figure 2). This phenomenon can result in an intake of the drug of such magnitude that it interferes with the vital functions of the organism, increasing the probability of death due to overdose, which is very common in heroin addicts (Siegel and Allan 1998).

Thus, an excessive demand for the homeostasis response endangers the balance of the affected system, which requires the participation of extra regulatory mechanisms. These extra regulatory mechanisms would modify the internal and external environment of the system, to induce and maintain a new equilibrium state of the organism, which has been labeled an allostatic state (Koob and Le Moal 2001). Thus, allostasis constitutes an emergency mechanism of regulation, lasting long-term, with the subject having a new (usually lower) set point. In the case of the consumption of substances of abuse, allostasis is reflected as a state in which the baseline loses its initial stability and becomes a descendant spiral, from the motivational point of view, producing a state of permanent dysphoria. The resulting

dysphoric response can only be counteracted or minimized by the presence of a rewarding stimulus of great magnitude, such as the drug (Koob and Le Moal 2001) (Figure 1).

Neural plasticity in the ventral tegmental area and its relationship with drug withdrawal

Several lines of evidence point to the VTA as the main neural substrate where the aversive information related to the withdrawal of a rewarding stimulus is processed (Frenois, Le Moine, and Cador 2005; Koob and Volkow 2016).

For approximately the last century, the ventral tegmental area (VTA) has been recognized as a nodal point for stimuli related to motivation (Olds and Milner, 1954). At first it was widely believed that VTA function was solely related to reward, and so the VTA and its connections to the nucleus accumbens and the prefrontal cortex were referred to as the mesolimbic reward system (Berridge, 2007). It was also believed that dopamine, the main neurotransmitter released by the VTA in the mesocorticolimbic pathway, was the substance of gratification (Berridge KC 2007). However, there are many studies showing that dopamine signaling is not necessary for gratification (Cannon and Palmiter 2003). Particularly, when organisms are naive in the consumption of substances of abuse, the reward mechanisms do not require dopamine (Laviolette et al. 2004). The gratification in naive individuals requires the activity of VTA GABA neurons projecting to a nucleus in the brainstem, the TPP (Bechara and van der Kooy, 1989). Without TPP activity, drug naïve individuals are unable to experience the rewarding properties of some of the most commonly used drugs, such as amphetamines, opiates and nicotine (Bechara and van der Kooy D 1989; Laviolette and van der Kooy, 2004). For these drugs, frequent and long-term administration is required for individuals to experience gratification through the dopaminergic system by way of negative reinforcement (Laviolette et al. 2004). However, this gratification is suggested to be the result of relieving the symptoms of aversion due to abstinence from the substance of abuse. If the withdrawal response is reduced by the administration of the drug, then the rewarding response requires activity in the TPP rather than the VTA dopamine system (Laviolette et al. 2004).

It has been proposed that the VTA is the location of the 'switch' mechanism between the two reward systems (dopaminergic and non-dopaminergic/TPP). For this switch to work, a dramatic change in the function of the VTA GABA-A receptors is required (Laviolette et al. 2004). Operating as a switch, the GABA-A receptor changes its function from its baseline (inhibitory effect on neuronal function) to excitatory. This allostatic change also occurs in other pathologies such as epilepsy and neuropathic pain. The change in the function of the GABA-A receptor produces a switch in the flow of information between the VTA and TPP systems. Specifically, when animals are naive, activation of GABA-A receptors located on VTA GABAergic neurons results in an inhibitory conductance mediated by Cl^- influx. The result of this GABA-A activity is activation of the TPP and inactivation of the VTA dopaminergic system. After the switch occurs from a nondependent to a drug-dependent motivational state, the inverted activity of the receptor (excitatory) produces the opposite result: when the subjects are drug-dependent, the VTA dopaminergic system is activated and the TPP is no longer involved (Laviolette et al. 2004). This change in GABA-A receptor function is due to the effect of a neurotrophic substance involved in stimulating the growth, survival and differentiation of neurons: BDNF (Vargas-Perez et al. 2009b). BDNF may reduce the levels of the potassium-chloride co-transporter KCC2, thereby increasing the intracellular chloride concentration. GABA-A receptor activation would then result in anions flooding out of the neuron (Ting-A-Kee et al. 2013). These changes would make the neuron's membrane potential more positive, or depolarized, relative to the resting membrane potential (Ting-A-Kee et al. 2013) (Figure 3). BDNF accumulates during periods of abstinence from a drug in the VTA, producing changes in the neuronal circuitry (Ting-A-Kee et al. 2013; Vargas-Perez et al. 2014, 2009b). BDNF is also implicated in learning in other areas of the brain, mainly in the hippocampus (Falkenberg et al. 1992). However, the BDNF-related exacerbation of neural plasticitity in GABAergic VTA neurons could cause a change in dopaminergic signaling leading to a missregulation in the mesolimbic system (Vargas-Perez et al. 2009b) (Figure 3).

Recent studies have shown that chronic administration of a drug is not necessary for an organism to become dependent (Vargas-Perez et al. 2009b): elevated levels of BDNF in the VTA are sufficient to produce a state of drug dependence (Ting-A-Kee et al. 2013; Vargas-Perez et al. 2009b). The levels of BDNF in the VTA can be elevated for different reasons, mainly due to the presence of chronic stress (Berton et al. 2006), or intense acute stress (Bennett and Lagopoulos 2014), and in general, by any event related to inflammatory processes inside or outside the VTA (Camargo 2016)

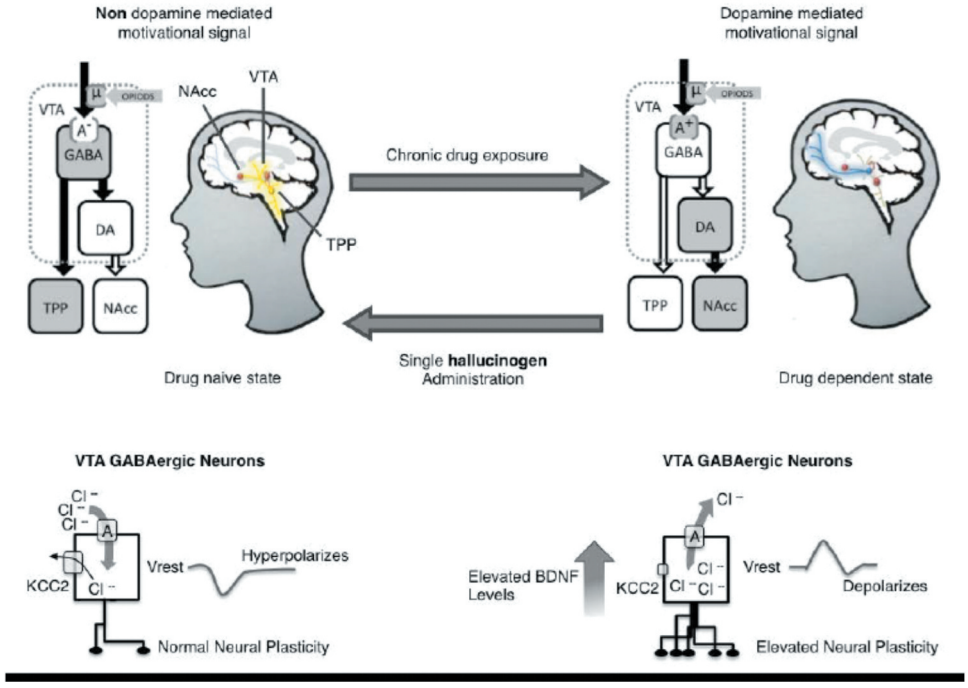

Figure 3. A. Transition to a dependent state is reverted by the administration of hallucinogens. The transition from a drug-naive to a drug-dependent and withdrawn state is a consequence of switching the neuronal substrates of drug motivation from a dopamine (DA) independent motivational system (involving the brainstem Tegmental Pedunculopontine Nucleus, TPP) to a dopamine-dependent pathway, which involves the Ventral Tegmental Area (VTA) and the Nucleus Accumbens (NAcc). A single (systemic or intra-VTA) administration of the hallucinogen psilacetin prevented and revert the switch from a drug-naive to a drug-dependent motivational state. B. Plastic Change in VTA GABAergic neurons according to the animal motivational states. When rats are opiate-dependent and in withdrawal, VTA GABA-A receptors switch their signalling properties from inhibitory to excitatory. BDNF promotes this switching mechanism. BDNF may reduce the levels of the potassium-chloride co-transporter KCC2, thereby increasing the intracellular chloride concentration. GABA-A receptor activation would then result in anions flooding out of the neuron. These changes would make the neuron's membrane potential more positive, or depolarized, relative to the resting membrane potential, underlying both the drug-dependent state and the aversion to withdrawal Cerveza de México, A.C

In addition to its function in the switch to a drug dependent state, BDNF has a fundamental role in the integration and consolidation of aversive motivational information (Vargas-Perez et al. 2014). In the absence of BDNF signaling, organisms are unable to perceive the aversion related to abstinence, although they do exhibit somatic symptoms of drug withdrawal (Vargas-Perez et al. 2014). The neuronal plasticity induced by BDNF involves the creation of new connections between neurons, and this neuronal plasticity is the basis of learning (Minichiello 2009). Each time BDNF is secreted, it supports the integration of stimuli, through the increased probability of forming new neuronal connections and/or the strengthening of existing synapses (Minichiello 2009). Thus, the VTA would be an area directly involved in the learning and consolidation of aversive information through mechanisms of neuronal plasticity induced by BDNF. Therefore, in a drug-dependent state, an uncontrolled increase in BDNF secretion would occur, and the resulting neuronal plasticity would lead to an increase in the representation of aversive stimuli, and even the generation of aversive states (withdrawal) in the absence of the drug.

The modulation of neuronal plasticity induced by BDNF is closely related to the regulation of the signaling of glutamate, the main excitatory neurotransmitter in the brain (Minichiello 2009). The subtle balance of glutamate transmission is crucial for the healthy functioning of an organism. Overactivation of glutamatergic signaling, called excitotoxicity (Manev et al. 1989), is related to various pathologies, from inflammatory processes and allergies to chronic degenerative diseases, including Alzheimer's disease, depression, Parkinson's disease, amyotrophic lateral sclerosis and epilepsy (Ishikawa 2013; Lai, Zhang, and Wang 2013; Lapidus, Soleimani, and Murrough 2013). In this way, the regulation of the glutamate signal is an opportunity for the development of therapies for diseases related to depressive states, and in general for other pathologies related to aberrant glutamatergic signaling.

Classic hallucinogenic substances for the treatment of drug withdrawal

Recent findings show that the administration of the hallucinogenic substance psilacetin blocks both the aversive conditioned response to drug withdrawal and the mechanism responsible for switching from a drug-naive to a drug-dependent motivational system, seemingly by preventing and reversing exacerbated BDNF-related plasticity in VTA GABAergic neurons (Vargas-Perez et al. 2017). This reduction of increased plasticity in VTA GABAergic neurons would be directly related to a decrease in the exacerbated inhibition that they exert over VTA dopaminergic neurons, consequently the inhibitory dopaminergic signaling on the mesolimbic system would be released and would in turn allow the relief of the negative symptoms associated with aversive motivation, such as the excessive craving related with the overactivity of the nucleus accumbens (Koob and Volkow 2016).

It has been suggested that activation of the serotonin (5-hydroxytryptamine, 5-HT) receptor type 2A (5-HT2A) can regulate the expression of BDNF differentially, depending on the neuronal group on which the receptor is located (Meller, Babity, and Grahame-Smith 2002; Vaidya et al. 1997). In particular, there is evidencet that agonists for these 5-HT2A receptors reduce the expression of BDNF in the GABAergic interneurons in the VTA (Hamon and Blier 2013), which are responsible for aversive motivation and the switch to a drug-dependent state. In addition, 5-HT2A receptors would regulate glutamatergic signaling by modulating the function and expression of glutamate receptors (Marek et al. 2000; Zhong, Yuen, and Yan 2008).

The hallucinogen substance psilacetin, the acetylated version of psilocybin, undergoes deacetylation to form psilocin and binds to the serotonin 5-HT2A receptor, causing a psychedelic effect (Nichols and Frescas 1999). It has been observed, using a place preference paradigm, that a single administration of psilacetin is sufficient to reverse and even prevent the motivational changes produced by the constant administration of a substance (nicotine, heroin and morphine) that lead to a state of dependence (Vargas-Perez et al. 2017). Likewise, a single systemic or intra-VTA administration of this 5-HT2A agonist can reverse the dependent state induced by the infusion of BDNF in the VTA (Vargas-Perez et al. 2017). In addition, as with the inhibition of BDNF signaling, a single systemic or intra-VTA administration of psilacetin was sufficient to block the aversion associated with drug withdrawal. However, these effects are not related to a general loss in the ability to detect aversive events, as animals pretreated with psilacetin were able to demonstrate conditioned place aversions induced by the opioid receptor antagonist naloxone, which produces aversions in both the drug-naıve and drug- dependent states (Vargas-Perez et al. 2017).

A remarkable finding is that a single systemic administration of psilacetin can prevent the effects of abstinence from the chronic administration of a drug even if it was injected one day before starting the treatment to induce dependence. Drug-naive animals pretreated with psilacetin did not demonstrate withdrawal aversions after chronic nicotine exposure with minipump implantations (Vargas-Perez et al. 2017). These results suggest that a single administration of a 5-HT2A agonist can lead to significant changes in the VTA, a nodal zone related to the management and consolidation of aversive information, thereby reversing and preventing induced pathologies that are due to an imbalance in neuronal plasticity (Vargas-Perez et al. 2017) (Figure 3).

The exact mechanisms by which 5-HT2A agonists act have not been properly clarified, but it is known that they can restore the changes induced by BDNF signaling. In addition, 5-HT2A receptors may be acting in concert, as they are inversely coupled with some of the brain's glutamate receptors,particularly the metabotropic glutamate receptor mGlu2 (Marek et al. 2000; Moreno et al. 2011, 2012). In this way, when a 5-HT2A receptor is stimulated, a glutamate receptor would be inactivated, and some of the aberrant glutamatergic signaling could be inhibited (Marek et al. 2000).

Recently, it has been observed that a key contribution of 5-HT2A agonists could be related to restore normal mitochondrial metabolism trough the action of the sigma-1 receptor (Sig-1 R) (Fontanilla et al. 2009; Frecska et al. 2013; Mavlyutov et al. 2017; Su, Hayashi, and Vaupel 2009). Particularly, mitochondrial competence is determinant for the neuronal resting membrane potential; metabolic stress leads to GABAergic dependent neuronal hyperactivity, which may initiate a cascade of pathological events (Holmgren et al. 2010) related to aversive motivation during drug dependent state.

Another possible route of action of 5-HT2A receptors is the long-term regulation of the expression of NMDA-like glutamate receptors (Zhong, Yuen, and Yan 2008). NMDA receptors are directly related to learning, particularly to the production and maintenance of potentiated glutamatergic signaling. Blockade of NMDA receptors with selective antagonists, such as ketamine, produces a relief of depressive symptoms almost

instantaneously after their administration (Lapidus, Soleimani, and Murrough 2013; Niciu et al. 2014). However, because the regulation of the NMDA receptor is at the synaptic level, its therapeutic effects are generally short-term (around a week), and at best a couple of months (Lapidus, Soleimani, and Murrough 2013; Niciu et al. 2014). On the other hand, the long-term effects (more than 6 months (Griffiths et al. 2011)) of the action of agonists at 5-HT2A receptors could be due to a modification in the genetic transcription of glutamatergic NMDA receptors (Yuen et al. 2008), however this hypothesis needs to be corroborated experimentally.

It is important to note that the expression of 5-HT2A receptors is increased in several pathologies, such as migraine (Srikiatkhachorn, Govitrapong, and Limthavon 1994), but in particular a dramatic increase in these receptors has been observed in the brains of patients with depressive disorders and in individuals who have committed suicide (Pandey et al. 2002). Moreover, the elevated expression of 5-HT2A receptors in the VTA increases the vulnerability of rats to the behavioral effects induced by cocaine, suggesting that 5-HT2A receptor in the VTA plays a role in regulation of responsiveness to stimulant substances (Herin et al. 2013). As occurs with other members of families of G-protein coupled receptors signaling through the 5-HT2A receptor produces a phenomenon of negative regulation of the same receptor (Buckholtz, Zhou, and Freedman 1988). Thus, each time these receptors are activated, there is a decrease in their expression, and the probability of their cell surface expression decreases (Buckholtz, Zhou, and Freedman 1988). In this way, the use of hallucinogenic substances decrease the production of 5-HT2A receptors (Raval et al. 2021), thus reversing the increase associated with pathological states, including depression and substance use.

The efficacy and effectiveness of 5-HT2A agonists as therapeutic agents against addiction has been documented in older anecdotal reports. However, after a pause of more than 40 years, scientific research on the utility of these substances has increased (Carhart-Harris and Goodwin 2017; DiVito and Leger 2020; Dos Santos Rg et al. 2016; Johnson, Garcia-Romeu, and Griffiths 2017; Mithoefer, Grob, and Brewerton 2016; Muttoni, Ardissino, and John 2019; Nichols, Johnson, and Nichols 2017; RG et al. 2019; Vargas-Perez and Doblin 2013). The implementation of classical hallucinogenic substances as a therapeutic aid or as a pharmacological therapy appears to be highly recommended. Preclinical data have shown that LSD and Psilocybin are able to reduce alcohol and tobacco use in addicted populations for more than 6 months, even after a single dose; and observational data suggest that Ibogaine and Ayahuasca have promising results in the treatment of various addictions, including alcohol and heroin addiction. Ketamine, which is able to diminish aberrant glutamatergic signaling, has been used to treat alcohol dependence and reduces cocaine self-administration in humans in laboratory settings. Accumulating clinical evidence has suggested that acute or repeated microdosing with these substances may have utility for treatment of some mental health disorders, including drug use and depression (DiVito and Leger 2020; Johnson et al. 2019; Morgan et al. 2017). However, due to their potent effects on cognition, the use of 5-HT2A agonists, mainly alkaloids from the group of tryptamines (such as DMT or psilocybin) and phenylethylamines (Mescaline and its derivatives), must be in an environment conducive to healing (Carhart-Harris and Goodwin 2017; Johnson, Garcia-Romeu, and Griffiths 2017; Johnson, Richards, and Griffiths 2008). The mental state, expectations and circumstances of the environment play a fundamental role in the experience resulting from the intake of these alkaloids, and their consumption in an inappropriate environment could lead to unpleasant consequences that compromise the mental stability of consumers (Johnson, Richards, and Griffiths 2008), even if they are taken in small, sub-hallucinogenic doses (Kuypers 2020; Petranker et al. 2020).

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