Neuropharmacology 76 (2014) 276–286

Contents lists available at SciVerse ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Invited review

Rapid, transient synaptic plasticity in addiction

Cassandra D. Gipson*, Yonatan M. Kupchik, Peter W. Kalivas

Department of Neurosciences, Medical University of South Carolina, 173 Ashley Ave., BSB 403, Charleston, SC 29425, USA

ARTICLE INFO

Article history:
Received 4 February 2013
Received in revised form
10 April 2013
Accepted 16 April 2013

Keywords:
Addiction
Synaptic plasticity
Relapse

ABSTRACT

Chronic use of addictive drugs produces enduring neuroadaptations in the corticostriatal glutamatergic brain circuitry. The nucleus accumbens (NAc), which integrates cortical information and regulates goal-directed behavior, undergoes long-term morphological and electrophysiological changes that may underlie the increased susceptibility for relapse in drug-experienced individuals even after long periods of withdrawal. Additionally, it has recently been shown that exposure to cues associated with drug use elicits rapid and transient morphological and electrophysiological changes in glutamatergic synapses in the NAc. This review highlights these dynamic drug-induced changes in this pathway that are specific to a drug seeking neuropathology, as well as how these changes impair normal information processing and thereby contribute to the uncontrollable motivation to relapse. Future directions for relapse prevention and pharmacotherapeutic targeting of the rapid, transient synaptic plasticity in relapse are discussed.

This article is part of a Special Issue entitled 'NIDA 40th Anniversary Issue'.

Published by Elsevier Ltd.

1. Introduction

Drug addiction is a leading cause of poor health and has enormous societal impact (Volkow et al., 2011). When investigating the neural mechanisms underlying various phenomena associated with drug addiction, glutamatergic input into the nucleus accumbens (NAc) emerges as a major regulator of addictive behavior. Long term changes in basal extracellular levels of glutamate (Baker et al., 2003; Peters et al., 2009; Wydra et al., 2013) and synaptic strength at glutamatergic synapses in the NAc (Boudreau and Wolf, 2005; Conrad et al., 2008; Gipson et al., 2013; Kourrich et al., 2007; Martin et al., 2006; Moussawi et al., 2009) are induced by chronic drug use. Although these slow and persistent changes may render the individual more vulnerable to relapse, they are not the mechanism triggering the relapse event.

A relapse event is frequently triggered by environmental cues associated with drug use, which rapidly initiate an urge to use drugs. This rapid change in behavior is driven by rapid, transient increases in synaptic strength in glutamatergic synapses between prefrontal cortex (PFC) afferents and medium spiny neurons (MSNs) of the NAc. Moreover, while the rapid, transient relapse-associated changes in excitatory synapses on MSNs are shared between classes of addictive drugs including nicotine, cocaine and heroin (Gipson et al., 2012, 2013; Shen et al., 2011), different classes of addictive drugs produce opposite long-term effects on excitatory transmission in the NAc. Specifically, repeated psychostimulant administration brings about an increase (Conrad et al., 2008; Gipson et al., 2012, 2013; Kourrich et al., 2007), and opioids cause a decrease in synaptic strength in the NAc as measured electrophysiologically and by dendritic spine morphology (Robinson and Kolb, 1999a; Shen et al., 2011; Spiga et al., 2005; but see Wu et al., 2012 who showed synaptic potentiation in the nucleus accumbens shell (NAshell) after withdrawal from morphine). It should be noted, however, that functional relevance of structural changes in spines remains difficult to interpret, as is discussed below in Section 1.3.

This review will focus on the glutamatergic input to the NAc and its involvement in drug relapse. We will discuss the sources of glutamatergic afferents to the NAc, as well as synaptic changes in glutamatergic input to the NAc. Special emphasis will be given to the newly discovered rapid, transient synaptic plasticity that underlies the initiation of relapse to drug seeking. Finally, we will discuss potential relevance to relapse prevention and pharmacotherapy development.

1.1. Glutamatergic projections to the nucleus accumbens involved in addiction and relapse

Glutamate neurotransmission in the NAc has been shown to underlie drug-seeking behavior, and changes in NAc glutamatergic transmission are thought to encode the transition from occasional use of drugs to the pathological inability to control drug-seeking

* Corresponding author. Tel.: +1 8438762246.
E-mail address: gipson@musc.edu (C.D. Gipson).

0028-3908/$ – see front matter Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.neuropharm.2013.04.032

behavior (Kalivas and Volkow, 2011; Kasanetz et al., 2010; Peters et al., 2009; Wolf and Ferrario, 2010). Neurons in the NAc receive convergent glutamatergic afferents from different cortical and subcortical regions (Fig. 1), including innervation by projections from the prefrontal cortex (PFC) (Berendse et al., 1992; Fuller et al., 1987; Gorelova and Yang, 1997; Papp et al., 2012; Reynolds and Zahm, 2005; Stefanik et al., 2012), the basolateral amygdala (BLA) (Groenewegen et al., 1980; McDonald, 1991a, b; Papp et al., 2012; Stuber et al., 2011), the ventral hippocampus (vHipp) (Britt et al., 2012; DeFrance et al., 1985; Groenewegen et al., 1987; Papp et al., 2012; Thompson and Swanson, 2010), the midline/intralaminar thalamic nuclei (Berendse and Groenewegen, 1990; Kelley and Stinus, 1984; Smith et al., 2004; Vertes et al., 2012), and the recently described glutamatergic neurons in the ventral tegmental area (VTA) (Gorelova et al., 2012; Hnasko et al., 2012; Yamaguchi et al., 2007, 2011). Interestingly, the different inputs are topographically arranged, such that each projection innervates different regions in the NAc, rather than diffusely innervating the entire NAc (Voorn et al., 2004). For example, afferents from the prelimbic and infralimbic subcompartments of the medial PFC are mostly segregated and project mainly to the NAcore and NAshell, respectively (Groenewegen et al., 1999; Wright and Groenewegen, 1995; Zahm, 2000); the projections from the BLA are compartmentally organized and more densely innervate the NAshell than the NAcore (Papp et al., 2012; Wright et al., 1996); the vHipp projections are most concentrated in the medial NAshell (Britt et al., 2012); and the paraventricular nucleus of the thalamus projects mainly to the NAshell (Papp et al., 2012; Smith et al., 2004). Microstructural studies show that all of the above projections synapse on spine heads of the GABAergic MSNs (Kita and Kitai, 1990; Meredith et al., 1990; Papp et al., 2012; Sesack and Grace, 2010). It should be noted that other studies also showed that in spite of the topographical segregation between different inputs in the NAc, individual MSNs can be innervated by projections from two or more different regions (Britt et al., 2012; French and Totterdell, 2002, 2003; Sesack and Grace, 2010; Stuber et al., 2011), thus implying that the MSNs have a role in integrating glutamatergic information from multiple sources.

While most research we describe below focuses on the projection from the PFC to NAc, other glutamatergic inputs are also implicated to a greater or lesser extent in the modulation of drug-seeking behavior. For example, the BLA integrates information regarding conditioned associations and affective drive (Sesack and Grace, 2010). Thus, activating the BLA and its projection to the NAc induces self-stimulation behavior (Stuber et al., 2011), while inhibiting this projection impairs drug-seeking induced by conditioned cues (Di Ciano and Everitt, 2004; Fuchs et al., 2007; McLaughlin and See, 2003; See et al., 2003). Similarly, activation of ventral hippocampal afferents to the NAshell promotes addiction-like behavior (Grace et al., 2007; Vorel et al., 2001), while inhibiting them attenuates drug-induced locomotion (Britt et al., 2012; Lodge and Grace, 2008).

A major glutamatergic input to the NAc comes from the PFC. This cortical region regulates goal-directed behaviors by integrating information from numerous brain regions and "making a decision" to execute an adaptive behavioral response (Balleine and O'Doherty, 2010; Killcross and Coutureau, 2003; Sharpe and Killcross, 2012; Smith et al., 2012). The medial portion of the PFC, which sends extensive projections to the NAc, is divided to dorsal prelimbic (PL), and ventral infralimbic (IL) regions. Although not completely segregated, the IL projects to the NAshell and has been associated with extinction of drug seeking, and the PL projects to the NAcore and is implicated in the execution of drug seeking (Capriles et al., 2003; Kalivas et al., 2005; LaLumiere et al., 2012; McFarland et al., 2004; McFarland and Kalivas, 2001; McLaughlin and See, 2003; Millan et al., 2011; Peters et al., 2009, 2008; Rocha and Kalivas, 2010; Stefanik et al., 2012; Van den Oever et al., 2008). Thus, inactivation of the PL prevents reinstated drug seeking in various animal models, while inactivation of the IL increases cocaine seeking. Interestingly, it has been shown that without a period of extinction training, inactivation of the IL can inhibit drug-seeking behavior (Koya et al., 2009). The IL-NAshell pathway appears to be involved in the learning of extinction rather than simply in the suppression of drug seeking behavior (LaLumiere et al., 2010); its activation reduces lever pressing by strengthening the extinction behavior (LaLumiere et al., 2012) when such behavior was learned. Thus, it is important to emphasize differences in various animal models when integrating mechanisms underlying relapse vulnerability.

Opposite roles for the PL and the IL, such as controlling drug seeking, have been reported for fear expression and extinction (Peters et al., 2009) as well as cue-induced cocaine seeking (McLaughlin and See, 2003). In fear conditioning experiments, the PL promoted fear behavior and its inhibition reduced expression of fear to contextual stimuli (Corcoran and Quirk, 2007; Peters et al., 2009; Sotres-Bayon and Quirk, 2010). The IL, on the other hand, is involved in fear extinction, and its inhibition decreases fear expression (Corcoran and Quirk, 2007; Peters et al., 2009; Sotres-Bayon and Quirk, 2010). The anatomically segregated pathways of the PL-to-NAcore and IL-to-NAshell projections, together with the results showing opposite involvement of PL and IL in the control of drug-seeking behavior, has led to a more simplified hypothesis of two parallel pathways in the control of drug-seeking behavior – the PL-to-NAcore pathway which promotes drug-seeking behavior and the IL-to-NAshell pathway which is responsible for the extinction of drug-seeking behavior (Peters et al., 2009). It should be noted, however, that studies examining the role of IL inactivation on reinstated drug seeking show inconsistent results, depending on the regimen used (Willcocks and McNally, 2013). Thus, IL inactivation has been shown to increase, decrease, or have no effect on reinstated drug seeking when using different behavioral paradigms, such as contextual renewal (Bossert et al., 2012; Willcocks and McNally, 2013), reinstatement after extinction (Peters et al., 2008), and cue-induced reinstatement after extinction from cocaine or methamphetamine self-administration (McLaughlin and See, 2003; Rocha and Kalivas, 2010).

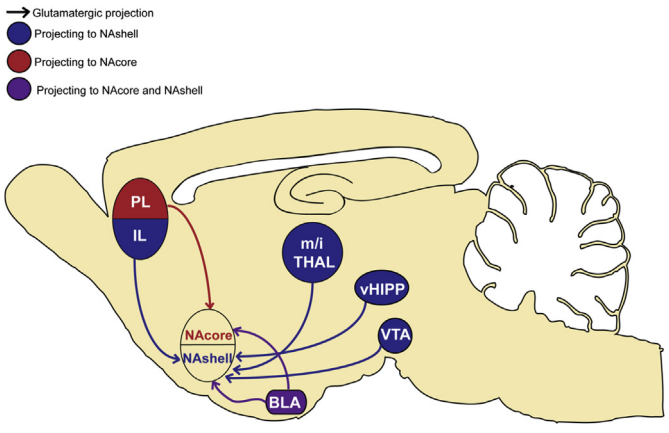

Fig. 1. Glutamatergic afferents to the nucleus accumbens involved in addictive behavior. While both nucleus accumbens subregions (NAcore and NAshell) receive input from all cortical regions, there is strong topographic bias. The NAcore receives glutamatergic input mainly from the prelimbic cortex (PL) and the basolateral amygdala (BLA), whereas the NAshell receives strong glutamatergic input from a larger number of sources, including the infralimbic cortex (IL), the ventral hippocampus (vHIPP), glutamatergic neurons in the ventral tegmental area (VTA), the midline/intralaminar thalamus nuclei (m/i THAL), and the BLA.