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Stress and VTA synapses: Implications for addiction and depression

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Abstract

While stressful experiences are a part of everyone's life, they can also exact a major toll on health. Stressful life experiences are associated with increased substance abuse, and there exists significant co-morbidity between mental illness and substance use disorders (Volkow & Li, 2004; Koob & Kreek, 2007; Sinha, 2008). The risk for development of mood or anxiety disorders after stress is positively associated with the risk for substance use disorders (Sinha, 2008), suggesting that there are common substrates for vulnerability to addictive and affective disorders. Understanding the molecular and physiological substrates of stress may lead to improved therapeutic interventions for the treatment of substance use disorders and mental illnesses.

Keywords

dopamine; reward; depression; synaptic plasticity; ventral tegmental area

Alterations in reward-related behaviors following stress suggest that the brain circuitry regulating reward and reinforcement may be a critical hub for the effects of stress on behavior. The ventral tegmental area (VTA) is a key player in the brain's reward system, and dysregulation of this brain region has long been implicated in both depression and addiction (Nestler & Carlezon, 2006; Fields *et al.*, 2007; Kauer & Malenka, 2007; Koob & Volkow, 2010; Wise & Morales, 2010; Luscher & Malenka, 2011). As the sites of information storage, synapses of the VTA are poised to be a crucial site of regulation of reward and aversion by stress. Here we will review recent literature on the role of VTA circuits and synapses in stress-related disorders.

I. VTA function and structure

Dopaminergic neurons in the VTA project to the prefrontal cortex and nucleus accumbens (NAc), as well as to the hypothalamus, amygdala, lateral habenula, pallidum, and bed nucleus of the stria terminalis (BNST) (Kauer & Malenka, 2007; Sesack & Grace, 2010). These neurons have long been implicated in rewarding and reinforcing processes. Release of

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dopamine from the VTA into the nucleus accumbens is necessary for the rewarding properties of natural stimuli required for survival, such as food and sex (Kelley & Berridge, 2002) as well as of drugs of abuse (Di Chiara & Imperato, 1988). Recent experiments utilizing optogenetic tools to activate VTA dopaminergic neurons selectively have demonstrated that phasic activity of these cells is sufficient to induce robust behavioral conditioning (Tsai *et al.*, 2009) and optical self-stimulation (Witten *et al.*, 2011). While this evidence is consistent with the conventional view of dopaminergic neuron activity signaling rewarding or incentive salient stimuli (Robinson & Berridge, 2000), aversive and stressful events are also clearly capable of enhancing dopaminergic function within the mesolimbic system (Tidey & Miczek, 1996; Anstrom & Woodward, 2005; Berton *et al.*, 2006; Brischoux *et al.*, 2009; Ungless *et al.*, 2010). For example, dopamine release in the NAc and prefrontal cortex increases during social threat (Tidey and Miczek, 1996), and VTA dopaminergic neurons are phasically excited by footshock and during acute restraint stress (Anstrom and Woodward, 2005; Brischoux et al., 2009). The precise meaning of neuronal signals within the mesolimbic dopamine system is still a topic of debate, but it is clear that this circuit is crucial for both rewarding and aversive experiences.

The VTA is made up of a mixture of dopaminergic, GABAergic, and glutamatergic neurons. Roughly 60–65% of these neurons are dopaminergic and 35% GABAergic, with a small population of glutamatergic neurons (Nair-Roberts *et al.*, 2008; Sesack & Grace, 2010). Additional complexity is added by the fact that dopaminergic neurons can co-release glutamate (Stuber *et al.*, 2010; El Mestikawy *et al.*, 2011; Hnasko *et al.*, 2012) or GABA (Tritsch *et al.*, 2012; Stamatakis *et al.*, 2013). Dopaminergic neurons of the VTA are highly heterogeneous anatomically and physiologically; however, recent work defining subclasses based on projection target has identified two useful broad divisions of dopaminergic cells (Ford *et al.*, 2006; Margolis *et al.*, 2006; Lammel *et al.*, 2008; Margolis *et al.*, 2008; Lammel *et al.*, 2011; Lammel *et al.*, 2012; Lammel *et al.*, 2013). In VTA slices, dopaminergic neurons known to project to the lateral shell of the nucleus accumbens exhibit the electrophysiological properties conventionally used to identify dopaminergic neurons, including a large h-current (I_h) that contributes to a slow, pacemaker firing rate. These neurons are found predominantly in the lateral portion of the VTA, and glutamatergic synapses on these cells have a low AMPA receptor/NMDA receptor ratio under basal conditions (AMPA/NMDA ratio) (Lammel *et al.*, 2013). In contrast, dopaminergic neurons projecting to the prefrontal cortex, basolateral amygdala, and core of the nucleus accumbens exhibit a negligible I_h, rapid firing rate, and a high AMPA/NMDA ratio under basal conditions, and are predominantly found in the medial VTA (Lammel *et al.*, 2013).

Both excitatory and inhibitory synapses control the firing rates and patterns of VTA dopaminergic neurons. *In vivo* recordings show that activation of glutamatergic neurons projecting from the prefrontal cortex to the VTA increases bursting of VTA DA neurons (Gariano & Groves, 1988; Murase *et al.*, 1993; Tong *et al.*, 1996). Bursting is typically not observed in dopaminergic neurons in the slice preparation, likely because excitatory afferents have been severed; however, bath application of NMDA induces bursting (Johnson *et al.*, 1992; Mereu *et al.*, 1997). GABAergic synapses also play a major role in shaping the activity of dopaminergic neurons. Both pharmacological and optogenetic studies

demonstrate that the firing rate of dopaminergic neurons is profoundly reduced by activation of $GABA_A$ receptors on these neurons (Johnson & North, 1992; Paladini & Tepper, 1999; Tan *et al.*, 2012; van Zessen *et al.*, 2012).

Not surprisingly, the subclasses of neurons projecting to NAc or prefrontal cortex (mPFC) receive distinct sets of afferent synapses with roles that are being unraveled using optogenetic activation. Dopaminergic neurons projecting to the accumbens shell receive excitatory glutamatergic and cholinergic inputs from the laterodorsal tegmental nucleus (LDT)(Lammel *et al.*, 2012), and inhibitory GABAergic input from the rostromedial tegmental nucleus (RMTg) (Goncalves *et al.*, 2012; Lammel *et al.*, 2012). The mPFC-projecting dopaminergic neurons, in contrast, receive glutamatergic input from the lateral habenula. The lateral habenula also sends excitatory projections to the RMTg, which in turn inhibits the NAc shell-projecting dopaminergic neurons (Lammel *et al.*, 2012; Stamatakis & Stuber, 2012). A minority of dopaminergic neurons found in the medial VTA also receive an inhibitory GABAergic input from the BNST. Although the projection target of these neurons has not been demonstrated, they lack I_h and are likely to be mPFC-projecting neurons (Jennings *et al.*, 2013).

In addition to these defined subcircuits of the VTA, several other regions strongly innervate the VTA, including glutamatergic inputs from the prefrontal cortex and lateral hypothalamus (Kempadoo *et al.*, 2013) and GABAergic inputs from the ventral pallidum (Hjelmstad *et al.*, 2013). A small population of dopaminergic neurons also receives excitatory inputs from the BNST (Jennings *et al.*, 2013). VTA dopaminergic neurons also receive inhibitory input from GABAergic neurons within the VTA (Tan *et al.*, 2012; van Zessen *et al.*, 2012). The nucleus accumbens sends a dense GABAergic projection to the VTA (Nauta *et al.*, 1978; Kalivas *et al.*, 1993), however recent optogenetic studies indicate that these projections make relatively weak $GABA_A$ synapses onto VTA dopaminergic neurons with no identified projection target (Bocklisch *et al.*, 2013) and make no $GABA_A$ or $GABA_B$ synapses onto dopaminergic neurons that project to the nucleus accumbens (Xia *et al.*, 2011). These findings are consistent with earlier literature suggesting that activating $GABA_A$ receptors in the VTA increases dopamine release locally and in nucleus accumbens (Kalivas *et al.*, 1990; Klitenick *et al.*, 1992; Xi & Stein, 1998), supporting the idea that activation of GABAergic afferents from the NAc primarily disinhibits VTA dopaminergic cells.

Considerably less is known about the connectivity and diversity of the non-dopaminergic neurons of the VTA, but GABAergic neurons within the VTA play a significant role in modulating dopaminergic cell activity and driving behavior. For example, optogenetic activation of VTA GABAergic neurons is sufficient to support conditioned place aversion and to interrupt reward consumption (Tan *et al.*, 2012; van Zessen *et al.*, 2012). VTA GABAergic neurons innervate local dopaminergic neurons, but also project to the nucleus accumbens, although there is debate over whether they synapse solely on cholinergic interneurons (Brown *et al.*, 2012) or on medium spiny neurons as well (Ishikawa *et al.*, 2013a; Ishikawa *et al.*, 2013b). VTA GABAergic neurons receive inhibitory input from medium spiny neurons of the nucleus accumbens (Xia *et al.*, 2011; Bocklisch *et al.*, 2013) and the BNST (Jennings *et al.*, 2013). In addition, roughly half of VTA GABAergic neurons have excitatory synapses originating in the BNST (Jennings *et al.*, 2013). Furthermore,

recent studies have identified a population of “hybrid” VTA neurons projecting to the lateral habenula that are positive for dopaminergic markers, but do not release detectable levels of dopamine. Instead, these neurons release GABA, which inhibits the lateral habenula and promotes reward seeking (Stamatakis *et al.*, 2013).

II. Projection-specific plasticity in reward and aversion

Repeated studies of synaptic plasticity in the VTA have consistently shown that glutamatergic inputs onto dopaminergic neurons are potentiated in brain slices from animals exposed *in vivo* to psychostimulants (Ungless *et al.*, 2001; Faleiro *et al.*, 2003; Saal *et al.*, 2003; Dong *et al.*, 2004; Bellone & Luscher, 2006; Argilli *et al.*, 2008; Chen *et al.*, 2008). Similar potentiation of glutamatergic synapses onto dopamine neurons is also observed after *in vivo* or *ex vivo* exposure to nicotine, morphine or ethanol (Mansvelder & McGehee, 2000; Saal *et al.*, 2003).

Cocaine-induced potentiation is mediated by an NMDAR-dependent increase in AMPA receptors at the synapse, reported as an increased AMPA/NMDA ratio (Ungless et al., 2001). This increase in AMPA/NMDA ratio corresponds with increased rectification of AMPA receptor currents and increased sensitivity to polyamines, suggesting an increase in GluA2-lacking AMPA receptors (Bellone & Luscher 2006; Argilli et al 2008). In addition, NMDA receptor currents induced by photo-uncaging at single synapses appear to be reduced by cocaine, further amplifying the change in AMPA/NMDA ratio (Mameli *et al.*, 2011), although no difference is observed in the response to exogenously applied NMDA (Ungless et al., 2001). NMDA currents in cocaine-treated animals also are more sensitive to ifenprodil, a selective inhibitor of GluN2B, and less sensitive to zinc, a selective inhibitor of GluN2A, suggesting an alteration in the ratio of GluN2A/GluN2B receptors (Yuan *et al.*, 2013). GluN2A/2B receptor switches often accompany significant changes in circuit properties, e.g. during developmental critical periods, powerfully altering synaptic Ca^{2+} entry and synaptic plasticity thresholds (Quinlan *et al.*, 1999; Kopp *et al.*, 2007). Cocaine treated animals appear to have increased insertion of GluN3a receptors, as indicated by reduced calcium permeability and magnesium sensitivity (Yuan *et al.*, 2013). Studies in GluN3a knockout animals and utilizing shRNA to GluN3a indicated that this subunit is required for the increase in AMPA/NMDA ratio following cocaine (Yuan *et al.*, 2013). These changes in both NMDARs and AMPARs significantly alter calcium permeability and calcium dynamics at the synapse, allowing stimulation protocols that are not sufficient for LTP induction in naïve animals to induce robust LTP following cocaine exposure (Mameli *et al.*, 2011).

LTP of glutamatergic synapses is long-lasting, persisting for a week after acute exposure to cocaine (Ungless *et al.*, 2001; Borgland *et al.*, 2004) and for at least three months after chronic cocaine self-administration (Chen *et al.*, 2008). While operant responding for naturally rewarding substances such as food or sucrose also potentiates glutamatergic synapses in the VTA, their effects are much shorter lived with AMPA/NMDA ratios returning to baseline levels between seven days and three weeks after the final self-administration session (Chen *et al.*, 2008).

Dopamine neurons with differing projection targets exhibit differential alterations in synaptic plasticity following rewarding or aversive stimuli (Lammel *et al.*, 2011). In the medial VTA, dopamine neurons projecting to the prefrontal cortex show a robust increase in AMPA/NMDA ratio in response to an aversive stimulus (hindpaw injection of formalin) but no change in response to a rewarding stimulus (single injection of cocaine). In contrast, VTA neurons projecting to the medial shell of the nucleus accumbens have an increased AMPA/NMDA ratio following cocaine injection, but do not change 24 hours after hindpaw formalin injection. Lateral VTA neurons, which project to the lateral shell of the nucleus accumbens, exhibit a moderate increase in AMPA/NMDA ratio after both rewarding and aversive stimuli (Lammel *et al.*, 2011). These data correspond nicely with the projection-specific functional role of dopamine neurons. Optogenetic stimulation of accumbens-projecting dopamine neurons supports robust place preference (Lammel *et al.*, 2012), suggesting that they contribute to reward. In contrast, activation of PFC-projecting dopamine neurons induces conditioned place aversion suggesting a role in aversion processing (Lammel *et al.*, 2012).

III. Stress and VTA synapses

Both excitatory and inhibitory synapses on VTA dopaminergic neurons express long-term potentiation (LTP) that is altered by exposure to acute stress(Saal *et al.*, 2003; Dong *et al.*, 2004; Niehaus *et al.*, 2010; Graziane *et al.*, 2013), reviewed in (Kauer & Malenka, 2007; Luscher & Malenka, 2011). Parallel changes seen after drug exposure and acute stress may provide a reason why acute stressors precipitate drug-seeking after abstinence. Like exposure to drugs of abuse, acute swim stress increases the AMPA/NMDA ratio of excitatory synapses on VTA dopaminergic neurons (Saal *et al.*, 2003; Dong *et al.*, 2004; Daftary *et al.*, 2009; Graziane *et al.*, 2013). This increase requires GluA1 receptors, and is dependent upon activation of NMDA receptors and glucocorticoid receptors (Saal et al., 2003; Dong et al., 2004) (Figure 1A). AMPA/NMDA ratios are potentiated as soon as 2 hours after stress, and remain potentiated for at least 24 hours (Daftary et al., 2009). Glucocorticoid receptor activation is sufficient to induce potentiation of these glutamatergic synapses, as either in vivo or in vitro dexamethasone increases AMPA/NMDA ratio (Daftary et al., 2009). Local block of both AMPARs and NMDARs in the VTA also prevents stress-induced dopamine efflux in the prefrontal cortex (Butts & Phillips, 2013).

In addition to glucocorticoids, other stress-modulating signaling molecules such as corticotrophin releasing factor (CRF) can regulate VTA functioning. CRF is a hypothalamic peptide that stimulates the hypothalamic-pituitary-adrenal stress response system and signals the effects of stress throughout the brain (Sarnyai *et al.*, 2001; Bale & Vale, 2004). The paraventricular nucleus of the hypothalamus, the central amygdala, and the BNST all send CRF-positive projections to the VTA (Rodaros *et al.*, 2007). While CRF-containing projections form both glutamatergic and GABAergic synapses, it appears that CRF-containing synapses on dopaminergic neurons are primarily glutamatergic (Tagliaferro & Morales, 2008). Both CRF_1R and CRF_2R receptors are found in the VTA (Van Pett *et al.*, 2000; Ungless *et al.*, 2003) and CRF promotes firing in both GABAergic and dopaminergic cells (Korotkova *et al.*, 2006). In dopaminergic neurons, the increase in firing rate occurs through alterations in the I_h (Wanat *et al.*, 2008). Bath application of CRF to VTA slices

also enhances NMDAR-mediated currents, but not AMPAR-mediated currents (Ungless *et al.*, 2003) (Figure 1B). This increase is mediated by CRF_2R receptors, and is dependent on activation of PKC.

Intriguingly, prior exposure to drugs of abuse enhances the effects of CRF on the VTA. Intra-VTA infusion of CRF increases extracellular glutamate levels in cocaine treated but not naïve rats (Wang *et al.*, 2005). Compared to cocaine-naïve rats, cocaine-experienced rats exhibit a greater magnitude and longer lasting potentiation of NMDAR currents induced by CRF (Hahn *et al.*, 2009). Unlike in naïve animals, in which CRF potentiates NMDAR currents solely through CRF_2R (Ungless *et al.*, 2003), the potentiation in cocaine-experienced rats is dependent on both CRF receptor subtypes. Furthermore, CRF potentiates AMPAR currents in cocaine-treated rats, but not in naïve animals. In rats that have self-administered cocaine, glutamatergic synapses on dopaminergic neurons are already potentiated, as evidenced by the increased AMPA/NMDA ratio (Chen *et al.*, 2008). That CRF is able to further potentiate these synapses suggests that CRF and cocaine self-administration potentiate distinct populations of glutamatergic synapses, or potentiate excitatory synapses through distinct mechanisms.

CRF also plays an important role in reinstatement of drug seeking after footshock. Footshock increases CRF levels in the VTA and causes a CRF-dependent increase in extracellular glutamate (Wang *et al.*, 2005). Intra-VTA infusion of CRF is also sufficient to reinstate cocaine seeking, an effect that is blocked by a glutamate receptor antagonist (Wang *et al.*, 2005). Footshock-induced reinstatement can be prevented by infusion of antagonists of CRF receptors or of AMPARs and NMDARs into the VTA (Wang *et al.*, 2005). Subsequent work demonstrated that a CRF_2R antagonist, but not a CRF_1R antagonist (Wang *et al.*, 2007) prevented footshock-induced reinstatement of cocaine seeking. Increased NMDAR currents and footshock-induced reinstatement also both require CRF binding protein (Ungless *et al.*, 2003; Wang *et al.*, 2007).

The dynorphin/kappa opioid receptor (KOR) system is an additional downstream mediator of the stress response that alters VTA synapses (reviewed in (Van't Veer & Carlezon, 2013). Afferents from several dynorphin-expressing brain regions including the nucleus accumbens, hypothalamus, amygdala and BNST project to the VTA (Fallon *et al.*, 1985; Meredith, 1999; Dong & Swanson, 2003; Chartoff *et al.*, 2009; Poulin *et al.*, 2009). KORs are expressed in the VTA (Speciale *et al.*, 1993; Arvidsson *et al.*, 1995; Mansour *et al.*, 1996) and dynorphin levels and kappa receptor phosphorylation are increased after stress (Nabeshima *et al.*, 1992; Land *et al.*, 2008). KORs have been strongly implicated in stress and aversion related behaviors (Bals-Kubik *et al.*, 1993; Beardsley *et al.*, 2005; Valdez *et al.*, 2007; Land *et al.*, 2008; Land *et al.*, 2009; Beardsley *et al.*, 2010; Bruchas *et al.*, 2010; Van't Veer & Carlezon, 2013), particularly in stress-induced drug seeking (McLaughlin *et al.*, 2003; Beardsley *et al.*, 2005; McLaughlin *et al.*, 2006; Carey *et al.*, 2007; Redila & Chavkin, 2008; Beardsley *et al.*, 2010; Sperling *et al.*, 2010; Graziane *et al.*, 2013; Van't Veer *et al.*, 2013)

KORs profoundly affect VTA synaptic transmission. Bath application of a KOR agonist to VTA slices transiently decreases EPSC amplitude on dopaminergic and GABAergic neurons

(Margolis *et al.*, 2005), IPSCs on BLA-projecting dopaminergic neurons (Ford *et al.*, 2006), and dopamine-mediated IPSCs (Ford *et al.*, 2007). Our recent studies show that activation of KORs also entirely blocks LTP at GABAergic synapses (LTP_{GABA}) on VTA dopaminergic neurons 24 hours after acute cold water swim stress (Nugent *et al.*, 2007; Nugent *et al.*, 2009; Niehaus *et al.*, 2010; Graziane *et al.*, 2013) (Figure 1C). However, administration of the KOR antagonist nor-BNI prevents the block of LTP_{GABA} by stress without preventing potentiation of excitatory synapses by stress. Linking this finding to drug self-administration, intra-VTA delivery of nor-BNI also prevents reinstatement of cocaine seeking after the same cold water swim stress (Graziane *et al.*, 2013). These data indicate that stress affects excitatory and inhibitory VTA synapses through distinct pathways, and that reinstatement can be prevented without restoring excitatory synapses to their pre-stress state.

Stress also alters delta opioid peptide effects on VTA synapses. In VTA slices from naïve animals, bath application of a delta opioid receptor (δOR) agonist depresses $GABA_A$ receptor-mediated IPSCs (Margolis *et al.*, 2011). In slices from animals exposed to footshock, however; a subset of cells exhibits an enhancement of $GABA_A$ synaptic currents following application of a δOR agonist. This enhancement primarily occurs in TH+/I_h+ dopamine neurons. Enhancement of IPSCs by the δOR agonist occurs via postsynaptic modifications, and is dependent on AKT-mediated trafficking of $GABA_A$ receptors to the cell surface.

Many intriguing questions remain regarding the regulation of VTA synapses by stress. In contrast to regulation of VTA synapses by cocaine, surprisingly little is known about the mechanism by which stress increases AMPA/NMDA ratios and if stress alters glutamate receptor subunit composition. Additionally, while early work found that either chronic restraint stress or chronic unpredictable stress increases expression of GluA1 and NMDAR1 subunits in VTA (Fitzgerald *et al.*, 1996), few studies since have investigated the effects of chronic stress on VTA synapses. Future studies in this area will be particularly valuable, given that human experience consists of a complex variety of stressors of varying intensities and duration. There is also very little known about effects of stress on projection-target specific dopamine neurons. As mentioned above, hindpaw formalin injection increases AMPA/NMDA ratio selectively on dopamine neurons projecting to the PFC, a circuit alteration that can be interpreted as a stress response. It will be of interest to ascertain whether similar neuroadaptations follow more complex stressors, such as those linked to reinstatement of drug seeking (cold water swim or footshock) or to chronic stress conditions, and whether stress-induced alteration in other forms of plasticity, such as plasticity of GABAergic synapses or potentiation of NMDA receptors by CRF is also restricted to defined subtypes of dopamine neurons.

IV. Stress and Addiction

Animal models have long suggested an interaction between stress and drug-seeking behavior. Acute and chronic stress protocols increase self-administration of psychostimulants, opiates, and, in some studies, alcohol (Hadaway *et al.*, 1979; Piazza *et al.*, 1990; Ramsey & Van Ree, 1993; Goeders & Guerin, 1994; Shaham & Stewart, 1994; Haney

et al., 1995; Miczek & Mutschler, 1996; Piazza & Le Moal, 1996; Kosten *et al.*, 2000; Sinha, 2001; Boyce-Rustay *et al.*, 2007; Moffett *et al.*, 2007; Sinha, 2008; Ambroggi *et al.*, 2009; Becker *et al.*, 2011). Additionally, stress reinstates drug-seeking in animals that have extinguished self-administration (Shaham *et al.*, 1994; Shaham & Stewart, 1995; Erb *et al.*, 1996; Le *et al.*, 1998; Shaham *et al.*, 2003; Conrad *et al.*, 2010). Taken together, these studies show that stress significantly alters an animal's behavior towards addictive drugs, both by increasing initial drug intake and by restoring previously-extinguished drug-seeking behavior.

Social defeat stress, a psychosocial stressor in which rodents are defeated by a conspecific aggressor, has been used as a model of escalated drug-seeking after stress (Miczek *et al.*, 2008). After exposure to an aggressor, defeated animals exhibit increased self-administration of cocaine during a 24 hour binge session and decreased latency to self-administration of cocaine during a binge session (Tidey & Miczek, 1997; Covington & Miczek, 2001; 2005). Defeated animals also have increased conditioned place preference for cocaine (McLaughlin *et al.*, 2006), and increased alcohol preference (Croft *et al.*, 2005; Dong *et al.*, 2011). Social defeat increases activity of dopaminergic neurons in the VTA, reflected in increased dopamine release in the nucleus accumbens (Tidey & Miczek, 1996). Furthermore, changes in behavioral responses to cocaine after social defeat can be reversed by intra-VTA infusion of an NMDAR antagonist or the CRF-1 antagonist, antalarmin (Croft *et al.*, 2005; Covington *et al.*, 2008).

The VTA is required for stress-induced reinstatement of drug seeking. Inactivation of the VTA with baclofen and muscimol prevents footshock induced reinstatement (McFarland *et al.*, 2004), and as discussed above, intra-VTA injections of a KOR antagonist also prevents swim stress-induced reinstatement (Graziane *et al.*, 2013). Similarly, the BNST-VTA pathway is important for reinstatement of place preference by swim stress (Briand *et al.*, 2010). A number of other areas essential for reinstatement including the BNST, PFC, and NAc, converge on the VTA, suggesting that the VTA may be a crucial intersection point between stress and drug seeking (McFarland *et al.*, 2004). Caution should be taken, however, in generalizing circuitry of reinstatement between distinct stressors, underscored by the apparent differences in reinstatement patterns after different stressors. For example, footshock causes a rapid, robust reinstatement (McFarland *et al.*, 2004; Wang *et al.*, 2005) that occurs in the same context where drugs are self-administered, while cold water swim stress, which is contextually and temporally separated from drug self-administration, induces a more mild reinstatement that lasts for several days (Conrad *et al.*, 2010).

Further investigation of mechanisms by which stress modifies synapses in the VTA may prove a rich vein for identifying novel treatment targets for addiction. Important molecular players in stress-induced drug seeking such as CRF receptors and the dynorphin-KOR system significantly alter excitatory and inhibitory synapses. Further defining these pathways, as well as finding new ways to manipulate VTA synapses, in animals and eventually in humans, may prove highly beneficial in treating addiction.

V. Depression

Anhedonia and appetite disturbance are core symptoms of depression that involve alterations in reward signaling, suggesting that stress-induced disruptions of the brain's reward circuitry may underlie some symptoms of depression (Nestler & Carlezon, 2006). Several studies of VTA dopaminergic neurons in depression have utilized the chronic social defeat stress model. In this model, repeated exposure to aggressive animals over a ten day period results in decreased social interaction, decreased sucrose preference, and a number of other behavioral abnormalities that may be related to major depressive disorder (Krishnan *et al.*, 2007). This behavioral model has several intriguing features. First, only a subset of animals exhibit these behavioral changes (termed susceptible animals), while the others are behaviorally unaffected (resilient), despite a fairly homogeneous genetic background. Second, the abnormal behaviors observed in susceptible animals can be reversed after a two-week but not a single-dose antidepressant treatment (Cao *et al.*, 2010). Many behavioral consequences of chronic social defeat stress seem to be encoded by alterations in VTA function.

Studies distinguishing between animals that are resilient and susceptible to social defeat have found that dopaminergic neurons in susceptible mice, but not resilient mice, exhibit increased firing rates (Berton *et al.*, 2006; Krishnan *et al.*, 2007; Cao *et al.*, 2010; Razzoli *et al.*, 2011). The alteration in firing rate is pathway specific, with accumbens-projecting neurons exhibiting an increased firing rate in susceptible animals and PFC-projecting neurons exhibiting a decreased firing rate (Chaudhury *et al.*, 2013) (recall that NAc shell-projecting dopaminergic neurons contribute to conditioned place reinforcement, while mPFC-projecting neurons contribute to conditioned place aversion (Lammel *et al.*, 2012)). Most significantly, normalizing the firing rate of dopaminergic neurons reverses the social interaction deficits and sucrose preference deficits of susceptible mice (Krishnan *et al.*, 2007; Cao *et al.*, 2010; Chaudhury *et al.*, 2013). These studies indicate a causal, projection-specific role for dopaminergic neurons in expression of anhedonic behavior after social defeat stress, and suggest the possibility that alterations in dopaminergic neurons and synapses on these cells also play a causal role in depression in human patients.

However, the role of VTA dopaminergic neurons in stress responding appears to be more complex. A recent study utilizing the chronic mild stress model in mice and rats over a longer time period found a markedly different result, instead reporting a decrease in dopaminergic neuron bursting after stress. Animals were exposed to randomly chosen unpredictable stressors such as crowding, isolation, and food deprivation, twice a day for eight to twelve weeks. Optogenetically stimulating VTA dopaminergic neurons reversed the stress-induced behavioral deficits in sucrose preference, the tail suspension test, and the forced swim test (Tye *et al.*, 2013). Although dopaminergic neurons in this study were not distinguished by projection target, the antidepressant effect of stimulating dopaminergic neurons was blocked by dopamine receptor antagonists in the NAc, suggesting that accumbens-projecting neurons played a role. Thus, in one study, susceptible mice that had undergone social defeat stress exhibited reduced dopamine cell firing rate and decreased sucrose preference, both alleviated by driving dopamine cell firing (Chaudhury et al., 2013), while in the second study, stressed mice instead had reduced dopamine neuron firing and

decreased sucrose preference, both alleviated by driving dopamine neuron firing (Tye et al., 2013). If driving dopaminergic neurons in opposite directions in fact restores sucrose preference, either the dopaminergic cells were in different “states” following the two distinct stress protocols, or the somewhat different temporal windows over which sucrose preference was tested contributed to the differences. Clearly, future work will help to identify the relevant differences between stress protocols, species, and methods of optogenetic stimulation. What is obvious from this body of work is the essential role of the VTA-nucleus accumbens circuit in stress-related and depression-related behaviors such as anhedonia.

It remains unknown whether VTA synapses are altered in depression models. The discovery that the NMDAR antagonist ketamine has a rapid antidepressant effect has increased interest in synaptic mechanisms of antidepressant action (Zarate *et al.*, 2006; Li *et al.*, 2010; Autry *et al.*, 2011; Mathews & Zarate, 2013). It will be intriguing to see whether VTA synapses are required for effectiveness of the rapid-acting antidepressants, and whether alterations in these synapses are necessary to promote the development of depressive-like behaviors in animal models. It will be of particular interest to investigate specific sources of synapses onto VTA dopaminergic neurons that are known to be implicated in depression. As one example, the lateral habenula, which sends projections to the VTA (Lammel et al., 2012), has been implicated in depression, and deep brain stimulation of this region was shown to induce remission in a patient with severe treatment refractory depression (Sartorius *et al.*, 2010). This role for the habenula in depression is also seen in animal models, where potentiated excitatory synapses on VTA-projecting neurons were seen in the rat acute and congenital learned helplessness models of depression (Li *et al.*, 2011). Deep brain stimulation in these animals, using the same protocol that showed efficacy in the human patient, suppressed excitatory synapses on habenula neurons and reversed the helpless phenotype of the rats (Li *et al.*, 2011).

VI. The VTA: a stress hub? Conclusions and future directions

Early on, it was clear that brief acute stress produces changes in VTA synapses that parallel those caused by addictive drugs (Saal et al., 2003). Since this time, the parallels have continued to be observed at the synaptic level, although it is clear that synapses on discrete subpopulations of dopamine neurons are differentially altered by drug exposure or by a brief stressor. Newer data addressing the links between behaviors and optogenetic activation of VTA dopamine neurons have clarified a key role of these neurons: to detect stress and modify behaviors accordingly. The management of stress by the reward/reinforcement circuitry may provide a unifying concept linking addiction-related behaviors with depression-related behaviors. In light of the high rate of co-morbidity between depression and addiction, targeting stress responses within the VTA may represent a highly useful therapeutic target for both disorders.

Chronic exposure to drugs of abuse persistently alters brain circuitry and synapses, perhaps accounting for the difficulty in returning to the pre-addicted state. Similarly, animal models of affective disorders have shown lasting differences in circuitry, and mood disorders are often chronic, recurrent illnesses. While reversing the cellular and molecular changes that occur after drug exposure or exposure to stressors may not be possible, there is growing

evidence that these changes throughout the brain can be circumvented or counterbalanced by therapeutic neuroadaptations or treatments (Mameli *et al.*, 2007; Wang *et al.*, 2007; Conrad *et al.*, 2008; Wee *et al.*, 2009; Russo *et al.*, 2012; Chaudhury *et al.*, 2013; Graziane *et al.*, 2013; Kallupi *et al.*, 2013; Loweth *et al.*, 2013; Tye *et al.*, 2013).

Stressors have multiple effects on cells and circuits. Some of these may be persistent and have negative consequences on behavior, e.g anhedonia or metabolic effects. However, some downstream sequelae of stress may be positive or protective (Russo *et al.*, 2012). The exact balance of these positive and negative consequences can vary considerably within a population. While all individuals experience the negative consequences of stress, the severity will depend on the individual. Conversely, the positive effects of stress occur independently of the negative effects, and do not necessarily reverse them. Some positive effects of stress may occur only a subset of individuals, granting them resilience to stressors. Resilience to stress may therefore represent a set of active mechanisms by which the negative consequences of stress can be compensated for and overcome, suggesting the importance of differences in individual behavioral responses to a given stress protocol in animal models of addiction and mood disorders. While studies continue to unravel mechanisms by which stress impacts behavior, stress is only one of several interacting factors contributing to the development of addiction and mental illness. Our growing understanding of genetic and environmental factors that contribute to predispositions to illness will allow us to integrate our understanding of how stressors act to trigger maladaptive responses.

Recent years have seen rapid and exciting advances in the neuroscience of stress, reward and aversion. This new knowledge has the potential to significantly impact our understanding of addiction and depression, but many questions remain. We are gaining a solid understanding of the regulation of synapses on VTA dopaminergic neurons, but much less is known about the synapses on other neurons of this region that have key functional roles in driving behavior. Optogenetic tools provide a tremendous opportunity for precise correlations of specific cell populations with complex behaviors, and will continue to identify neural pathways and cell types involved in specific behaviors. The complexity of the data already arising from optogenetic studies of the mesolimbic dopamine circuitry simply emphasizes the complexity of the behaviors relevant to human addiction and depression. As tools and approaches are refined, we will develop a more sophisticated understanding of how to modify circuits that have been altered in the addicted or depressed brain, and how to limit the negative effects of further stressful experience. Pinpointing signaling molecules and receptors that control synapses within these specific circuits will provide pharmacological tools as well as potential sites for deep brain and transcranial magnetic stimulation through which these circuits can be targeted for treatment of disease.

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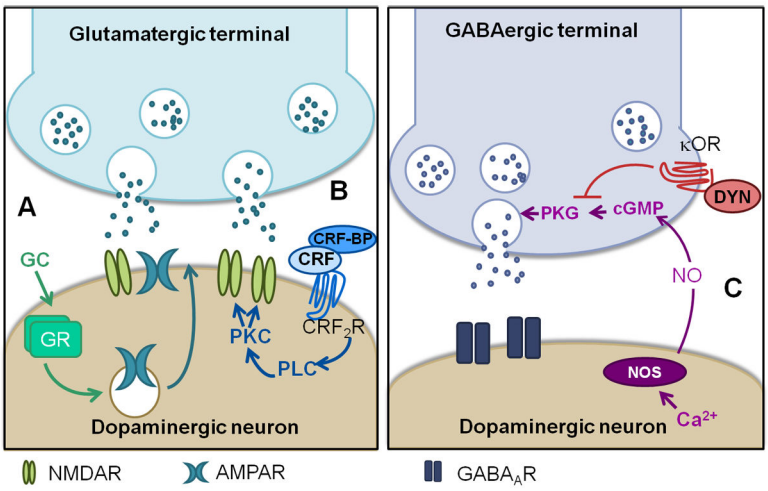

Figure 1.

Modulation of VTA synaptic plasticity by stress systems. A) At excitatory synapses, stress-induced activation of glucocorticoid receptors leads to an increase in the AMPA and NMDA ratio. B) CRF potentiates NMDA currents through activation of CRF_2 receptors and downstream activation of PLC and PKC. C) Inhibitory synapses are potentiated via the retrograde messenger nitric oxide and activation of cGMP signaling. This plasticity is blocked by stress through activation of kappa opioid receptors. From (Saal *et al.*, 2003; Ungless *et al.*, 2003; Nugent *et al.*, 2007; Daftary *et al.*, 2009; Nugent *et al.*, 2009; Niehaus *et al.*, 2010; Graziane *et al.*, 2013)

GC: glucocorticoid, GR: glucocorticoid receptor, CRF: corticotrophin releasing factor, CRF-BP: CRF-binding protein, CRF_2R: CRF receptor type 2, PLC: phospholipase C, PKC: protein kinase C,NOS: nitric oxide synathase, NO: nitric oxide, cGMP: cyclic guanosine monophosphate, κOR: kappa opioid receptor, dyn: dynorphin, PKG: protein kinase G