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REVIEW

Ventral tegmental area dopamine revisited: effects of acute and repeated stress

Elizabeth N. Holly[1,3] · **Klaus A. Miczek**[1,2]

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Abstract Aversive events rapidly and potently excite certain dopamine neurons in the ventral tegmental area (VTA), promoting phasic increases in the medial prefrontal cortex and nucleus accumbens. This is in apparent contradiction to a wealth of literature demonstrating that most VTA dopamine neurons are strongly activated by reward and reward-predictive cues while inhibited by aversive stimuli. How can these divergent processes both be mediated by VTA dopamine neurons? The answer may lie within the functional and anatomical heterogeneity of the VTA. We focus on VTA heterogeneity in anatomy, neurochemistry, electrophysiology, and afferent/efferent connectivity. Second, recent evidence for a critical role of VTA dopamine neurons in response to both acute and repeated stress will be discussed. Understanding which dopamine neurons are activated by stress, the neural mechanisms driving the activation, and where these neurons project will provide valuable insight into how stress can promote psychiatric disorders associated with the dopamine system, such as addiction and depression.

Keywords Stress · Aversion · Dopamine · Ventral tegmental area

✉ Elizabeth N. Holly
eholly@mit.edu

[1] Department of Psychology, Tufts University, 530 Boston Avenue, Medford, MA 02155, USA

[2] Department of Neuroscience, Tufts University, 145 Harrison Avenue, Boston, MA 02111, USA

[3] Present address: McGovern Institute for Brain Research and Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, MA, USA

Introduction

Both aversive and rewarding stimuli rapidly and potently excite dopamine neurons in the ventral tegmental area (VTA). Furthermore, these seemingly opposite experiences interact with each other at both a neural and behavioral level. A history of exposure to aversive stimuli is strongly associated with later addictive behavior, with both clinical and preclinical work demonstrating that stress plays a powerful role in the initiation, escalation, and relapse to drug abuse (Shaham et al. 2000; Sinha 2007, 2009). However, the converse is also true—a history of cocaine self-administration results in greater susceptibility to chronic social defeat stress in mice (Covington et al. 2011).

As aversion/stress and reward are interacting at a behavioral level, it is logical that they interact at a basic neural level as well. Indeed, it appears that intersecting as opposed to parallel neural circuitry may be driving these two distinct experiences of aversion and reward, both mediated by the mesocorticolimbic dopamine system. Classic evidence has established a clear function of mesocorticolimbic dopamine in rewarding and reinforcing processes, and a key role of mesocorticolimbic dopamine in the response to acute and repeated stress is becoming increasingly apparent.

Unfortunately, with this rapidly growing body of research on the role of dopamine in the effects of stressful and aversive stimuli, the nature, schedule, and intensity of stressors are often overlooked. This may stem from a lack of consensus on the definition of stress. When Selye popularized the term "stress" as a biomedical construct in 1936, he proposed that stress was any demand on the body that resulted in adaptation but that all stressors resulted in identical non-specific physiological responses (Selye 1936). However, over the last 80 years, it has become quite evident that while there may be some non-specific responses, different stressors/aversive

stimuli can result in distinct, specific responses. Mason (1971) first questioned Selye's hypothesis of non-specific responses, noting that stressors could increase, decrease, or not change hypothalamic–pituitary–adrenal (HPA) axis activity. Chrousos and Gold (1992) expanded upon this, defining stress as a state that resulted from a threat to homeostasis, yielding behavioral and physiological adaptations that could be specific to the stressor or non-specific when the threat to homeostasis reaches a homeostatic threshold. McEwen (1998) applied the concept of allostasis as an active adaptive process to maintain stability through change. For the purposes of this review, we choose to define stress as a threat to homeostasis caused by an aversive event (stressor), either physical or perceived, which results in *specific* allostatic compensatory responses (Pacak and Palkovits 2001).

Prior work from our and other laboratories has unambiguously demonstrated that different schedules, intensities, or modalities of stressor presentation can result in dramatically different behavioral and physiological responses. For example, intermittent/episodic and chronic social defeat engenders opposite effects on subsequent cocaine-stimulated dopamine increases in the nucleus accumbens shell (NAcSh) as well as cocaine self-administration (Miczek et al. 2011). But, how does stressor specificity interact with later reward-related behaviors? And, how is mesocorticolimbic dopamine poised to play a key interactive role between the seemingly opposite experiences of reward and aversion?

We begin by briefly reviewing the structure, connectivity, and function of VTA dopamine neurons, followed by evidence for VTA dopamine neuron activation and adaptation in response to both acute and repeated stress, with careful attention paid to the nature, schedule, and intensity of the stressor. The structure, connectivity, and function of VTA dopamine neurons with specific regard to reward-related behaviors have been thoroughly reviewed previously (Ikemoto 2007), so that will be summarized here only briefly. Ultimately, we propose that VTA dopamine neurons rapidly fire in response to both reward and aversion, and certain intensities and schedules of stress can induce neuroadaptations within these neurons to result in intensified responses to later aversive *and* rewarding stimulation.

Heterogeneity in structure and function of VTA dopamine neurons

Prior to the advancement of current labeling techniques, the VTA was not considered a separate structure from the cell bodies of the substantia nigra (SN). The first anatomical description of the VTA was made with Golgi and Nissl preparations by Tsai (1925a, b), who concluded that the cell-free space overlying the sulcus, along with smaller cell size and close relationship to the tracti mammillo- and olfactotegmentalis, warranted a separation from the SN. Later anatomical investigations validated Tsai's initial hypothesis that this area contains a discrete population of dopaminergic cells serving a distinct function from SN dopaminergic neurons, leading other researchers to initially term the region the ventral tegmental area of Tsai.

Dopamine cells have been isolated in many animals, including fish (Lefranc et al. 1969), birds (Fuxe and Ljunggren 1965), rats (Carlsson et al. 1965), and other mammals (Fuxe and Owman 1965), but the VTA as a structure appears to be evolutionarily conserved only in higher-order vertebrates. Lower vertebrates do not show a defined VTA, with the "peripeduncular area" containing both dopamine and serotonin cells (Dube and Parent 1982), and broader development of the VTA observed in only a few teleosts and reptiles (Oades and Halliday 1987). However, there is a high degree of similarity between the VTA of mammals, including opossum (Crutcher and Humbertson 1978), rat (Lindvall and Bjorklund 1974; Phillipson 1979a, b, c), rabbit (Blessing et al. 1978), dog (Shimada et al. 1976), cat (Pin et al. 1968; Poitras and Parent 1978; Taber 1961), non-human primate (Felten et al. 1974; Garver and Sladek 1975; Hubbard and Di Carlo 1974; Jacobowitz and MacLean 1978; Tanaka et al. 1982), and human (Bogerts 1981; Bogerts et al. 1983; Nobin and Bjorklund 1973; Olson et al. 1973). Further, the number of VTA dopamine neurons increases with phylogenetic order, such that Balb/C mice have an estimated 25,000 dopamine neurons, albino rats 40,000, and a 33-year-old man 450,000 (German et al. 1983).

Regardless of homology between higher-order species, researchers have struggled to clearly define the boundaries and function of the VTA. As reviewed below, the VTA is a heterogeneous structure in regards to cytoarchitecture, neurochemical, and electrophysiological profiles, and afferent/efferent connections, so it is not surprising that there is evidence that VTA dopamine neurons may serve multiple functions, such as reward and aversion.

Heterogeneity in dopaminergic cytoarchitecture

The VTA is characterized by considerable heterogeneity in dopaminergic cytoarchitecture. In mammalian species, the VTA is comprised of four major zones or subnuclei (Fig. 1). The rostrally located parafasciculus retroflexus area (PFR) and caudally located ventral tegmental tail (VTT) contain few dopaminergic cell bodies, while the paranigral nucleus (PN) and parabrachial pigmented area (PBP) are rich in dopaminergic neurons. Additionally, the adjacent midline nuclei—the caudal linear nucleus (CLi), interfasicular nucleus (IF), and rostral linear nucleus of the raphe (RLi)—are often considered VTA subregions (Oades and Halliday 1987; Swanson 1982). However, even within these subregions, dopaminergic

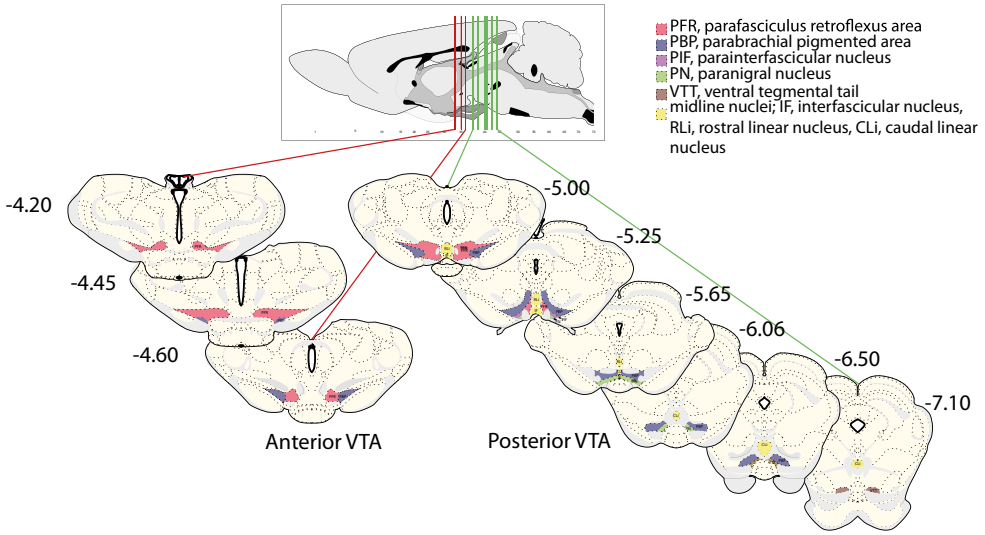

Fig. 1 Subregional distinctions in the VTA. Coronal sections are arranged from anterior (−4.20) to posterior (−7.10) from bregma. The division between anterior and posterior VTA is drawn between the interpeduncular nucleus and the interpeduncular fossa. PFR (*red*), parafasciculus retroflexus area; PBP (*blue*), parabrachial pigmented area; PIF (*purple*), parainterfascicular nucleus; PN (*green*), paranigral nucleus; VTT (*brown*), ventral tegmental tail; midline nuclei (*yellow*); IF, interfascicular nucleus; RLi, rostral linear nucleus; CLi, caudal linear nucleus (Color figure online)

cell body characteristics are still not homogeneous (for thorough review, see Ikemoto 2007).

As described in detail by Ikemoto (2007), the PFR, restricted to the anterior portion of the VTA, contains a low density of small- to medium-sized dopaminergic cell bodies, which show light to moderate immunoreactivity for tyrosine hydroxylase (TH, the rate-limiting enzyme in dopamine biosynthesis, used as a marker of dopaminergic cells) and are continuous with dopaminergic cell bodies in the posterior hypothalamic area. The VTT also has a low density of dopaminergic cell bodies, which are small and moderately stained for TH. The densest TH-positive staining is found in the middle two thirds of the VTA, divided into the PN and PBP (some have characterized an additional subregion separating the PN and PBP, the paraintrafasicular nucleus, PIF). The PBP begins to emerge in the anterior VTA but spans the majority of the posterior VTA. The PBP is heterogeneous in terms of cytoarchitecture, leading to inconsistently defined borders in the rat and mouse. The PBP contains both large and medium cell bodies, with no unified orientation. Within the anterior VTA, the PBP contains large, intensely stained cell bodies, which are continuous with the anterior SN pars compacta. In the posterior VTA, the PBP is located dorsolateral to the PN and contains cell bodies and fibers that form a net-like structure. The PN is restricted to the posterior VTA and contains TH-positive cell bodies oriented mediolaterally, tilting toward the IF, that are relatively medium in size and medium to darkly stained. The midline nuclei, which are often considered part of the VTA, are also rich in TH-positive cell bodies. Most notably, the IF contains the densest population of dopaminergic cell bodies in the ventral midbrain. The CLi also contains a dense population of relatively homogenous dopaminergic cell bodies, which are medium in size and medium-dark in TH staining.

It is clear from this and other existing immunohistochemical data that a great deal of cytoarchitectonic heterogeneity exists not only within the VTA but also within specific subregions of the VTA. Not only has this led to a difficulty in establishing clear boundaries of the VTA and its subregions, but this heterogeneity in structure points to further heterogeneity in neurochemical and electrophysiological profiles, as well as overall function.

Heterogeneity in neurochemical profile

VTA neurons also differ in their neurotransmitter profile. VTA neurons have typically been classified as principal (primarily dopaminergic), secondary (GABAergic), or tertiary (other) on the basis of immunohistochemistry for TH, as well as electrophysiological and pharmacological properties (Cameron et al. 1997; Grace and Onn 1989; Johnson and North 1992). Tertiary neurons are hyperpolarized by opioids and serotonin, and while one third of these have been identified as atypical-dopaminergic, the neurochemical profile of the remaining two thirds has yet to be clearly characterized (Cameron et al. 1997; Lammel et al. 2014). Altogether, the VTA is comprised of approximately 65 % dopaminergic neurons, 35 % GABAergic neurons, and less than 3 % glutamatergic neurons (Nair-Roberts et al. 2008; Sesack and Grace 2010). However, it should be noted that VTA dopamine neurons projecting to the NAc can also co-release glutamate (Hnasko et al. 2012; Stuber et al. 2010), further highlighting the neurochemical heterogeneity within the region.

Heterogeneity in electrophysiological profile

Despite this immense anatomical and neurochemical heterogeneity in the VTA, it has until recently been common practice of most in vivo electrophysiological studies to consider VTA dopamine neurons as a single homogenous population (reviewed in Lammel et al. 2014; Ungless and Grace 2012). As in vivo electrophysiological measurements do not allow for direct confirmation of the neurochemical identity of the neurons being recorded, neurons are putatively characterized based on standard classification criteria: broad action potentials, low-frequency pacemaker activity, D2-agonist-induced hyperpolarization, and/or the presence of large *Ih* currents generated by hyperpolarization-activated cyclic nucleotide–regulated cation channels, or HCN channels (Kitai et al. 1999; Ungless and Grace 2012).

However, it has been established that these conventional criteria are not necessarily reliable (as reviewed extensively in Ungless and Grace 2012). Briefly, the presence of large *Ih* currents within the VTA can be observed in non-dopaminergic neurons (Margolis et al. 2006; Margolis et al. 2008; Zhang et al. 2010). Furthermore, some verified VTA dopamine neurons are not responsive to dopamine bath application (Bannon and Roth 1983; Lammel et al. 2008) and others have very small or negligible *Ih* currents (Brischoux et al. 2009; Ford et al. 2006; Hnasko et al. 2012; Jones and Kauer 1999; Lammel et al. 2008; Lammel et al. 2011; Margolis et al. 2006; Zhang et al. 2010). As such, it appears that VTA dopamine neuron heterogeneity extends to electrophysiological profiles as well. Unfortunately, this electrophysiological heterogeneity has resulted in some populations of dopamine neurons going unstudied in many prior reports, confounding previous conclusions drawn about VTA dopamine neuron function.

Not surprisingly, it appears that these electrophysiologically distinct dopamine neurons are located within discrete anatomical subregions of the VTA. Most in vivo electrophysiological studies have used these conventional classification methods described above to identify putative dopamine neurons, and as such have primarily focused on dorsal portions of the VTA, specifically within a region medial to the medial terminal nucleus of the accessory optical tract (Lammel et al. 2014; Ungless et al. 2010; Zhang et al. 2010), where putative dopamine neurons fit these conventional criteria. Thus, the studies focusing on the function of these specific, "conventional" dopamine neurons in this small portion of the VTA may not be applicable to "non-conventional" dopamine neurons in other subregions of the VTA. These other regions of the VTA, such as the ventromedial posterior VTA consisting of the PN and PBP, have been largely ignored as many of the dopaminergic neurons in this area do not conform to established conventional criteria such as large *Ih* (Lammel et al. 2008). Therefore, it has been proposed that while the correlation between *Ih* and dopamine phenotype may be high in the commonly targeted dorsolateral region of the VTA (specifically the anterior PBP), other subregions such as the PN and posterior PBP, which have been largely ignored, contain dopamine neurons with a distinct electrophysiological profile. Electrophysiological characterization of dopaminergic neurons within these other anatomical subregions of the VTA should be elucidated in future work, as these areas have been implicated in vastly different behavioral functions (discussed in section Heterogeneity in VTA dopamine neuron function).

Heterogeneity in efferent connections

VTA connectivity is also critical because recent anatomical studies demonstrate localized projection targets of VTA subregions, which in turn have important behavioral and functional implications. VTA dopamine neurons project throughout the brain in a non-overlapping mediolateral topography at an approximate 45° angle to the midline (Albanese and Minciacchi 1983; Fallon 1981; Ikemoto 2007). While few have closely examined the heterogeneity in efferent and afferent connections within VTA subregions, the most intensively mapped connections have been between the VTA subregions and the striatum. Ikemoto (2007) demonstrated that dopamine-rich cell bodies in the ventromedially located PN and dorsoposteromedial portions of the PBP selectively project to the medial nucleus accumbens (NAc) shell, medial prefrontal cortex (mPFC), and medial olfactory tubercle (OT, Fig. 2) regions heavily implicated in reward and reward processing (although these regions certainly mediate other functions as well). Along the mediolateral projection topography, lateral PBP dopamine neurons send dense projections to the ventrolateral striatum, which has been less heavily implicated in reward-related functions (Ikemoto 2007). The PFR and VTT do not contain dense dopamine cell bodies, but the sparse dopamine cell bodies of the PFR selectively project to the diagonal band. Projection targets of the midline nuclei are also distinct, with dopamine neurons in the IF projecting selectively to the dorsomedial NAc shell, and RLi to the diagonal band and pallidal zone of the OT (Ikemoto 2007). Future work needs to evaluate VTA heterogeneity in other dopamine projection sites, such as the mPFC and BLA.

Heterogeneity in afferent connections

There may also be subregional differences in afferent connectivity to the VTA, although this has not yet been thoroughly investigated. VTA dopamine neurons receive innervation from widespread regions throughout the brain. The direct monosynaptic inputs to midbrain dopamine neurons have been thoroughly mapped recently (Watabe-Uchida et al. 2012). Notably, VTA dopaminergic neurons receive the most innervation from the ventral striatum, particularly the NAc,

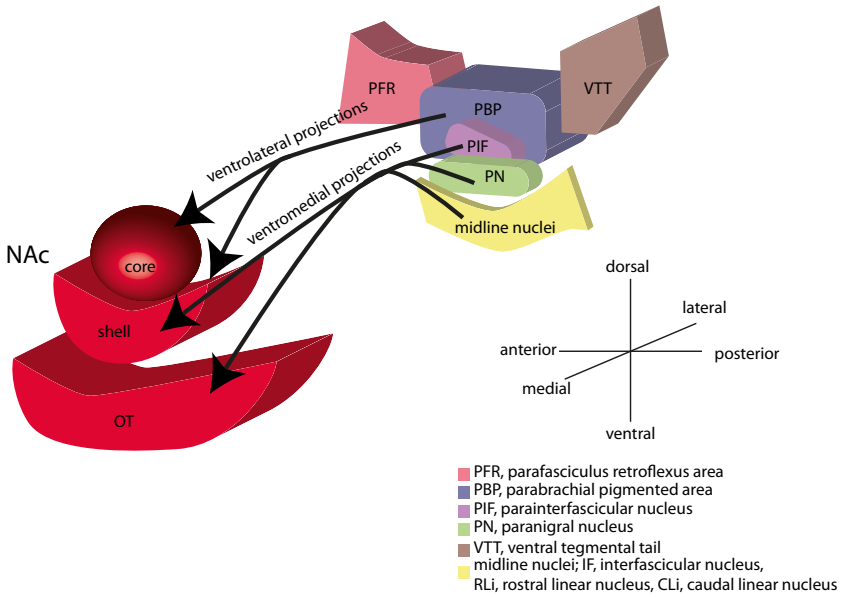

Fig. 2 Heterogeneity in efferent connections of the VTA to the ventral striatum. Striatal efferents project along a mediolateral trajectory to the nucleus accumbens (NAc) and olfactory tubercle (OT), such that laterally located parabrachial pigmented area (PBP, *blue*) dopamine neurons send projections to the lateral NAc core and shell, while the medially located paraintrafascicular nucleus (PIF, *purple*), paranigral nucleus (PN, *green*), and midline nuclei (*yellow*) project to the medial NAc shell and medial OT (Color figure online)

while the densest innervation originates from the dorsal raphe nucleus (DRN). NAc cells projecting to VTA dopamine neurons form extremely dense patches within the NAc. Moreover, these projection cells are morphologically distinct from NAc GABAergic medium spiny neurons, indicating distinct heterogeneity in the ventral striatum. Future circuit tracing experiments should investigate whether this afferent heterogeneity extends to the VTA.

Heterogeneity in VTA dopamine neuron function

The aforementioned heterogeneity in anatomy, neurochemistry, electrophysiological profile, and connectivity points to diversity in the overall behavioral functions VTA dopamine neurons mediate. As many of the dopamine projection targets of the VTA have been heavily implicated in reward, there has been considerable attention paid to VTA dopamine neurons in these processes. Both natural rewards (Berridge 1996) and drugs of abuse (Di Chiara and Imperato 1988) stimulate release of dopamine from VTA neurons projecting to the NAc, leading to a well-accepted hypothesis that this connection at least partially drives reward-related functions.

However, recent evidence has also shown heterogeneity within these projection targets in terms of reward-related function. Cocaine infused directly into the medial NAcSh produces significantly greater changes in locomotion compared to cocaine infused directly into the lateral NAcSh (Ikemoto 2002, 2007). Rats will selectively self-administer cocaine and amphetamine into the medial but not lateral NAcSh (Ikemoto 2002; Ikemoto and Donahue 2005), with similar differences observed between the medial and lateral OT (Ikemoto 2002; Ikemoto and Donahue 2005). Therefore, it is not surprising that the posteromedial VTA, centered around the PN and posteromedial PBP and projecting to the medial NAcSh and OT, has been shown to also play a stronger role in reward processes than the anterior and lateral portions of the VTA (Rodd-Henricks et al. 2002; Sellings and Clarke 2003; Sellings et al. 2006). Specifically, cocaine, nicotine, opiates, ethanol, and cannabinoids are all selectively self-administered into the posterior but not anterior VTA (Ikemoto et al. 2006; Ikemoto and Wise 2002; Rodd et al. 2005; Rodd-Henricks et al. 2000; Zangen et al. 2006).

This mesocorticolimbic dopamine circuitry stemming from the VTA and projecting to the ventral striatum and medial prefrontal cortex thus plays a fundamental role in reward. This is paralleled by subsequent reports that rewards, as well as their predictive cues, can elicit strong phasic firing within the dopamine cell bodies of the VTA (Schultz 1997, 1998). These pioneering findings have led to a prominent hypothesis that this system primarily serves to mediate reward, hedonia, and related energizing processes (but see Salamone and Correa 2012). Given this overwhelming evidence, it was initially surprising and controversial to many researchers that VTA dopamine could be involved in stress and other aversive events (Thierry et al. 1976), which will be the focus of the remainder of this review.

Effects of acute stress on VTA dopamine neuron activity

Electrophysiological studies have shown that aversive stimuli inhibit putative VTA dopamine neuron firing (e.g., Mantz et al. 1989; Mirenowicz and Schultz 1996; Schultz and Romo 1987; Ungless et al. 2004). However, microdialysis studies examining extracellular dopamine and its metabolites

collected over minutes and hours have found a robust dopaminergic increase during stress in VTA projection targets. Various stressors such as restraint, footshock, tail pinch/shock, social threat, and others potently increase extracellular dopamine in the NAc and mPFC (section Microdialysis evidence; see Tables 1, 2, 3, 4, 5, 6, 7, 8, and 9 and Fig. 3). Across these studies, the nature and degree of the dopaminergic increase vary according to stressor and intensity. Recent electrophysiological studies have also found a discrete subset of VTA dopamine neurons that increase firing in response to aversive stimulation, corroborating the observed microdialysis results (section Electrophysiological evidence). Additional studies have found long-lasting neuroadaptive changes on VTA dopamine neurons after a single stress exposure, highlighting that acute stress can alter VTA dopamine neuron responsivity to future stimulation, whether by additional stressors or rewards (section Evidence for neuroadaptations on VTA dopamine neurons).

Microdialysis evidence

Early postmortem studies found altered dopamine and dopamine metabolite concentrations in brains of rodents following stress (Deutch et al. 1991; Deutch et al. 1985; Dunn and File 1983; Fadda et al. 1978; Kramarcy et al. 1984). With advances in microdialysis techniques to monitor in vivo extracellular monamine levels in awake, freely moving animals in the late 1980s, researchers began to more directly assess dopamine in response to a variety of stressors.

Table 1 Effects of restraint stress on extracellular dopamine concentrations in the NAc

Reference	Species	Stressor parameters	Stressor pattern	Sample length (min)	Max DA (%BL)	Time course of DA efflux	Increase at termination?	Additional findings
Imperato et al. (1989)	SD rat	90 min	Acute	10	145 %	Immediate increase, returned to baseline by 70 min	Not measured	Corticosterone also increased DA
Imperato et al. (1990)	SD rat	120 min	Acute	10	150 %	Immediate increase, peaked at 30–40 min, returned to baseline by 80 min	Not measured	Prevented by 5HT3 antagonist but not diazepam
Imperato et al. (1991)	SD rat	120 min	Acute	10	150 %	Immediate increase, peaked at 30 min, gradual decrease to baseline by 80 min, increase at release	Yes	Exogenous corticosterone did not increase DA
Puglisi-Allegra et al. (1991)	SD rat	240 min	Acute	10	140 %	Immediate increase, peaked at 30 min, gradual return to baseline by 80 min, increase at release	Yes	
Imperato et al. (1992)	SD rat	60 min for 6 consecutive days, repeated after 3 days	Repeated	10	150 %	Day 1: immediate rise, peak at 20 min, gradual decrease towards baseline, but increase at release. Days 2, 3, and 4: blunted initial response, no change at termination response. Day 7: same as day 1	Yes	Decrease in dopaminergic tone as well
Imperato et al. (1993)	SD rat	120 min, with 5 prior days of 60 min	Acute and repeated	10	CTRL 150 %, prev. stress 70 %	Previously non-stressed: immediate increase, peaks at 20 and 30 min, gradual return to baseline by 50 min. Previously stressed: initially stay at baseline, drop below baseline 80–120 min into restraint	Not measured	
Lillrank et al. (1999)	SD rat	30 min	Acute	15	130 %	No changes during restraint, peak only observed 60 min after termination	Yes	NAc core, not shell, and probe too long (included more than core)
Jackson and Moghaddam (2004)	SD rat	10 min	Twice, 3 h apart	10	125 %	Both exposures showed similar increase, peaking at 20 and 30 min, return to baseline by 60 min, increase at termination	Yes	

NAc nucleus accumbens, *DA* dopamine, *BL* baseline, *SD* Sprague–Dawley

Table 2 Effects of restraint and immobilization stress on extracellular dopamine in the mPFC

Reference	Species	Stressor parameters	Stressor pattern	Sample length (min)	Max DA (%BL)	Time course of DA efflux	Increase at termination?	Additional findings
Matuszewich et al. (2002)	SD rat	Immobilization 60 min	Acute	20	175 %	Immediate maximal increase during first 20 min, then back to baseline for duration	No	MDMA pretreatment blocked effect
Pozzi et al. (2002)	SD rat	Immobilization 120 min	Acute	20	250 %	Immediate maximal increase, returned to baseline within 100 min; increase again 20–60 min after release, although not as high as before	Yes	
Swanson et al. (2004)	SD rat	Immobilization 30 min	Acute	30	189 %	Increased to 150 % during stress, but peaked at 189 % after termination, with gradual return to baseline by 90 min after initiation of stressor	Yes	mglu2/3 agonist blocks increases in both dopamine and noradrenaline
Renoldi and Invernizzi (2006)	CD-COBS rats, Mongolian Gerbils	Immobilization 40 min	Acute	20	188 %, 31-6 %	Rats showed immediate increase during immobilization, which remained elevated 40 min after stressor termination. Gerbils showed immediate increase, peaking in second half of stressor presentation, and returning to baseline 40 min after stressor termination	[a]	
Arriaga-Avila et al. (2014)	Wistar rat, female	Immobilization 30 min	Acute	15	200 %, n/a	Increased to 200 % in second half of stress in virgin females, returning to baseline by 45 min after termination. No effect observed in non-virgins (lactating dams)	[a]	
Imperato et al. (1991)	SD rat	Restraint 120 min	Acute	10	180 %	Immediate increase, peaking 30 min into restraint, and returning to baseline after 90 min. Increase again at termination	Yes	Looked at corticosterone—adrenalectomy had no effect, and exogenous corticosterone did not affect dopamine release
Cuadra et al. (1999)	Wistar rat	Restraint 60 min	Acute, with 1 week of chronic variable stress	30	146 %, 17-7 %	No CVS group increased dopamine beginning at 60 min, with maximal increase at 120 min, never returning to baseline. CVS group showed maximal (177 %) increase at 120 min, returning to baseline at 300 min.	[a]	Reversed by naloxone
Cuadra et al. (2001)	Wistar rat	Restraint 60 min	Acute, 1 week chronic variable stress	30	139 %, 18-9 %	Without CVS, dopamine increased gradually during restraint, peaking (139 %) and sustained for duration of sampling.	[a]	

Table 2 (continued)

Reference	Species	Stressor parameters	Stressor pattern	Sample length (min)	Max DA (%BL)	Time course of DA efflux	Increase at termination?	Additional findings
						CVS group also increased gradually and peaked (189 %) 30 min after termination without returning to baseline		
Mokler et al. (2007)	SD rat	Restraint 20 min	Acute, some with prior prenatal malnourishment	20	150 %, n/a	Controls 150 % during stress, immediately back to baseline on termination. Malnourished did not increase dopamine during stress, but were significantly attenuated 100–160 min after release	No	
Garrido et al. (2013)	Wistar rat	Restraint 20 min	Acute	20	165 %	Immediate increase in response to stress, remained elevated, back to baseline by 40 min after termination	[a]	
Jackson and Moghaddam (2004)	SD rat	Restraint 10 min	Repeated after 3 h	10	140 %	Immediate increase during first exposure, sustained for one sample after termination, then back to baseline. Second exposure showed habituated da response	[a]	
Ventura et al. (2013)	NMRI outbred female mice	Restraint 180 min	Acute	20	165 %	Remained elevated for 120 min of restraint	Did not measure	

[a] Dopamine did not return to baseline prior to stressor termination and so cannot be assessed

mPFC medial prefrontal cortex, *DA* dopamine, *BL* baseline, *SD* Sprague–Dawley, *CVS* chronic variable stress, *n/a* not available

Imperato and colleagues (1989) were among the first to use microdialysis to demonstrate a significant increase in extracellular dopamine in response to restraint stress. She and others have found that restraint stress reliably increases extracellular dopamine in the NAc (Table 1) and mPFC (Table 2) to roughly equivalent degrees (average maximal percent change from baseline from Tables 1 and 2 142.5 and 155 % for NAc and mPFC, respectively).

Studies examining extracellular dopamine in the mPFC in response to immobilization have found a slightly greater response (average maximal percent change from baseline 200 %, Table 2), indicating that there may be a difference in severity between these two similar stressors. This may be explained by a confound within the methods of the experiments utilizing restraint stress. All but two studies (Garrido et al. 2013; Mokler et al. 2007) were conducted in the light phase of the light–dark cycle. Restraint stress during the dark (active) phase results in significantly reduced body weight gain and development of stomach ulcers, whereas no such effects are produced by restraint during the light (inactive) phase (Koolhaas et al. 2011; Pare and Glavin 1986; Rybkin et al. 1997). Wild Norway rats spend the light phase hiding in narrow burrow systems (Koolhaas et al. 2011), so restraint may be a less potent stressor during this phase. Rather than the physical compression used in restraint stress, immobilization involves restricting paw movement in a less constrained manner and as such may be a more powerful stressor during the light phase.

While some studies have demonstrated that dopamine levels in both the NAc and mPFC remain elevated for the duration of restraint (Cuadra et al. 2001; Cuadra et al. 1999; Garrido et al. 2013; Jackson and Moghaddam 2004; Mokler et al. 2007), when restraint is prolonged (>60 min), dopamine levels return to baseline within 70–120 min (Imperato et al. 1992; Imperato et al. 1993; Imperato et al. 1991; Imperato et al. 1989; Imperato et al. 1990; Puglisi-Allegra et al. 1991). Thus, there appears to be a habituation of the dopamine response upon extended stressor presentation. However, as

Table 3 Effects of footshock stress on extracellular dopamine in the NAc

Reference	Species	Stressor parameters	Stressor pattern	Sample length (min)	Max DA (%BL)	Time course of DA efflux	Increase at termination?	Additional findings
Sorg and Kalivas (1991)	SD rat	0.55 mA/200 ms/s for 20 min	Acute	20	150 %	Increase with stressor, sustained for 60 min after termination	[a]	Stress cross-sensitized to increased response to cocaine, but not vice versa
Young et al. (1993)	SD rat	0.33 mA, 1-s train of 6-ms pulses, 25 Hz, 5-min intervals	Acute and conditioned	10	193 %	In non-conditioned rats, immediate increase during footshock, returning to baseline immediately after. Efflux augmented (to above 300 %) with cs pairing	No	
Kalivas and Duffy (1995)	SD rat	0.35 mA/200 ms/s for 20 min	Acute	20	230 %	Increased only at termination, sustained for an additional 20 min	Yes	No increases observed in NAc core
Saulskaya and Marsden (1995)	Lister rat	0.5 mA for 1 s×10, 1 min apart, paired with tone	Acute	20	135 %	Increased during footshock, remained elevated for 20 min after termination	[a]	Intra-NAc dizocilpine did not affect initial response, but prevented sustained increase. AMPA antagonist no effect
Motzo et al. (1996)	SD rat	0.2 mA for 500 ms every secons, 8 min	Acute	10	160 %	Increased to 120 % during stressor, maximal increase at termination, remained elevated for 40 min after termination of stressor	[a]	ICV allopregnanalone dose-dependently reduced basal dopamine and prevented mPFC and NAc footshock-induced increases. ICV midazolam similar effect but with greater potency
Fulford and Marsden (1998)	Lister rat	0.5 mA for 1 s×10, 1 min apart, paired with tone	Acute, one group reared in isolation	20	173 %, 200 %	Group reared rats showed delayed dopamine response to footshock, reaching max (173 %) 60 min after stress initiation. Isolation reared showed immediate increase in NAc dopamine (200 %), which remained elevated for 120 min. Both showed conditioned response, but more so in isolation reared	[a]	
Takahashi et al. (1998)	Wistar rat	0.1 mA for 10 s, once per minute for 30 min	Acute	30	167 %	Did not increase during stress, but sustained increase at termination	Yes	Prevented by chronic nicotine; stress resulted in nicotine cross-sensitization
Yamanashi et al. (2001)	SD rat	0.4 mA, 200 ms, 1 Hz, 20 min	Acute	20	140 %	Immediate increase during stress, gradually increased, return to baseline by 120 min after stress initiation	[a]	Pretreatment with mecamylamine and diazepam each attenuated dopamine release
Young (2004)	SD rat	0.3 mA, 1-s train of 6-ms pulses, 25 Hz; 4 presentations at 5-min intervals, repeated day 2. Separate group footshock paired with tone, and tone alone on day 2	Repeated	1	175 %, 225 %	Day 1: immediate increase during footshock (max 175 %), which returned to baseline immediately upon termination, no habituation. Effect identical on day 2. Augmented when paired with tone (225 %), and tone itself elicited 40 % increase	No	

[a] Dopamine did not return to baseline prior to stressor termination and so cannot be assessed

NAc nucleus accumbens, *DA* dopamine, *BL* baseline, *SD* Sprague–Dawley, *CS* conditioned stimulus, *ICV* intra-cerebroventricular

Table 4 Effects of footshock stress on extracellular dopamine in the mPFC

Reference	Species	Stressor parameters	Stressor pattern	Sample length (min)	Max DA (%BL)	Time course of DA efflux	Increase at termination?	Additional findings
Feenstra et al. (2001)	Wistar rat	Aversive conditioning: 10-s white noise (25 dB) immediately followed by 0.3-mA footshock repeatedly presented 9x (conditioned group), or non-paired presentations (pseudo group) or no conditioning (control group). Later tested just CS	Acute	16	250 %, 200 %, n/a	Significantly increased immediately in aversive conditioning (250 %) and pseudo conditioning (200 %) groups, gradually returning to baseline, with no changes in control group. Presentation of CS alone resulted in 150 % increase in aversive group only	[a]	
Hamamura and Fibiger (1993)	Wistar rat	0.4 mA, 10-s duration, 50-s interval, 20 min	Acute, with possible prior injection stress (14 days)	20	225 %	Immediate increase during footshock, slowly returning to baseline by 40 min after termination	[a]	
Sorg and Kalivas (1993)	SD rat	0.55 mA/200 ms/s, 20 min	Acute	20	200 %	Initial increase to 150 % baseline, 200 % in sample after termination, returning to baseline 40 min after termination	[a]	Cocaine pretreatment abolished stress-induced DA response, and footshock reduced response to subsequent acute cocaine
Dazzi et al. (1995)	SD rat	0.2 mA for 500 ms every second for 8 min	Acute	10	190 %	Initial increase to 140 % baseline, peaking at termination, returning to baseline 20 min after termination. Repetition one hour later resulted in smaller increase (125 %)	[a]	
Motzo et al. (1996)	SD rat	0.2 mA for 500 ms, every second, for 8 min	Acute	10	165 %	Immediate rise to 125 % during footshock, peaking at termination, returning to baseline 30 min after termination	[a]	ICV allopregnanalone and midazolam dose dependently reduced basal DA and prevented stress-induced DA increase, midazolam with a greater potency
Dazzi et al. (2001a)	SD rat	0.2 mA for 500 ms, every 2, for 8 min	Acute	20	190 %	Immediate increase during stress, no longer statistically significant 10 min later	Sample included both stress and termination	2-week (but not single dose) imipramine or mirtazapine reduced and completely antagonized (respectively) increase in DA during footshock
Wedzony et al. (1996)	Wistar rat	0.5 mA/200 ms for 5 s twice during one 25-min session, then removal, brought back to context 25 min later with no shocks	Acute	25	150 %, 140 %	Increase to 150 % during footshock, immediately returning to baseline, and increase to 140 % basal levels in response to context	no	Diazepam decreased outflow and blunted conditioned stress response. Ipsapirone and buspirone abolished stress-evoked elevation in dopamine
Dazzi et al. (2001b)	SD rat	0.2 mA for 500 ms every second for 8 min	Acute	20	190 %	Increased during stressor, immediately returned to baseline	Sample included both stress and termination	2-week imipramine or mirtazapine inhibited or prevented (respectively) stress-induced DA increase.
Dazzi et al. (2004)	SD rat	0.2 mA for 500 ms every second for 8 min	Acute	20	190 %	Increased during stress, immediately returning to baseline in next sample	Sample included both stress and termination	2-week olanzapine or clozapine prevented or significantly inhibited, respectively, stress-induced DA increase; haloperidol had no effect

[a] Dopamine did not return to baseline prior to stressor termination and so cannot be assessed

mPFC medial prefrontal cortex, *DA* dopamine, *BL* baseline, *SD* Sprague–Dawley, *CS* conditioned stimulus, *n/a* not available

Table 5 Effect of tail pinch stress on extracellular dopamine in the NAc

Reference	Species	Stressor parameters	Stressor pattern	Sample length (min)	Max DA (%BL)	Time course of DA efflux	Increase at termination?	Additional findings
Klitenick et al. (1996)	SD rat	10 min	Acute	10	121 %	Increase during and sample after release, gradual return to baseline	[a]	Corticosterone increased DA response by 50 %
King et al. (1997)	SD rat	30 min	Acute	15	120 %	Peaked during tail pressure, slow return to baseline after removal	[a]	No change in NAc core; DA efflux potentiated with mPFC lesions
Rouge-Pont et al. (1998)	SD rat	10 min	Acute	20	130 %	Immediate rise during stress, gradual decrease back to baseline	[a]	Blocking corticosterone decreased stress-induced DA release
Di Chiara et al. (1999)	SD rat	10 min, repeated after 120 min	Acute, one group with 4wks CMS	10	75 %, 130 %	Non-stressed showed 25 % decrease immediately after tail first tail pinch, no change after second. prior CMS peak DA during first tail pinch, returned to baseline 80 min after release, similar effect during second tail pinch	[a]	
Naef et al. (2013)	SD rat	30 min	Repeated 5 days	15	175 %, 240 %	Day 1: immediate increase, slightly decreased after release, back to baseline following sample. day 5: sensitized response, peak during stressor, return to baseline 45 min after termination, but spiked again 90 min later	[a]	

[a] Dopamine did not return to baseline prior to stressor termination and so cannot be assessed

NAc nucleus accumbens, *DA* dopamine, *BL* baseline, *SD* Sprague–Dawley, *CMS* chronic mild stress

restraint is the only stressor examined in microdialysis studies to date that is amenable to such prolonged presentation, it is not clear if this habituation would extend to other types of stress.

Mild footshock has also been shown to potently increase dopamine in both the NAc (Table 3) and mPFC (Table 4) to comparable degrees (average maximal percent change from baseline 169.22 and 194 % for NAc and mPFC, respectively). Notably, all reports of microdialysis during footshock stress have used less than 0.55-mA intensity, generally considered to be mild. Future work could examine the relationship between footshock intensity and extracellular dopamine in the NAc and mPFC. Mild to moderate tailshock (1.0 mA) also produces significant increases in extracellular dopamine in the mPFC (Table 7, average maximal percent change from baseline 169 %). Like footshock, the effects of varying intensities of tailshock on extracellular mesocorticolimbic dopamine efflux have not been examined and could be the focus of future work.

Microdialysis has also been used to examine dopamine responses to acute tail pinch (Tables 5 and 6). Unlike restraint and footshock, tail pinch stress may differentially increase extracellular dopamine in the NAc and mPFC, with greater dopamine efflux observed in the mPFC (average maximal percent change from baseline 124 and 184 % for NAc and mPFC, respectively). As none of the studies examined the dopamine response in both the NAc and mPFC, it is possible that there are differences in intensity of tail pinch pressure between labs. However, it may also be the case that very mild tail pinch stress is insufficient to activate VTA dopamine neurons, and the mPFC dopamine response is due to another function, such as novelty.

Likewise, handling, often considered a very mild stressor, has differential effects on extracellular dopamine in the NAc and mPFC (average maximal percent change from baseline 126 and 197 % for NAc and mPFC, respectively, Tables 8 and 9). Duration of handling stress does not appear to reliably affect extracellular dopamine concentrations, but there may be strain differences in reactivity to handling, as the greatest changes in mPFC dopamine were observed in Wistar as opposed to Sprague–Dawley rats.

However, not all stressors examined have produced increases in extracellular NAc and mPFC DA. Acute forced swim stress, often thought to be a much milder stressor than footshock and restraint stress (Jordan et al. 1994), does not alter extracellular dopamine in the NAc or the mPFC (Azzi et al. 1998; Jordan et al. 1994). Likewise, the similarly mild stressor of airpuff to the face or low-dose cytokine (IL-8) injection does

Table 6 Effect of tail pinch stress on extracellular dopamine in the mPFC

Reference	Species	Stressor parameters	Stressor pattern	Sample length (min)	Max DA (%BL)	Time course of DA efflux	Increase at termination?	Additional findings
Jedema and Grace (2003)	SD rat	20 min	Acute	20	180 %	Increased during stress, peaked immediately after termination, returned to baseline by 60 min after termination	[a]	AP5 did not blunt response, but CNQX did
Finlay et al. (1995)	SD rat	30 min	Acute, with prior chronic cold exposure	30	154 %	Increased during stressor, remained elevated for 30 min after termination, no difference between controls and CCE	[a]	Diazepam decreased basal DA and attenuated stress evoked increase in control rats only (no effect of diazepam in CCE group)
Venator et al. (1999)	SD rat	30 min	Acute	15	200 %	Immediate increase, remained elevated after cessation, returning to baseline 60 min later	[a]	
Mendlin et al. (1999)	SD rat	20 min	Acute, repeated once	20	144 %	Immediate increase, returned to baseline 40 min after sample termination	[a]	Raclopride augmented effect
Di Chiara et al. (1999)	SD rat	10 min	Acute, repeated once, one group with prior CMS	10	175 %, 225 %	Controls showed significant increase (175 %) during tail pinch, slowly decreasing back to baseline by 30 min after release, same time course and magnitude with second m pinch. CMS animals showed significantly greater magnitude (225 %) with similar time course	[a]	
Page and Lucki (2002)	SD rat	20 min	Acute	20	n/a	No change	n/a	
Butts et al. (2011)	SD rat	15 min	Acute	15	300 %	Immediate increase, gradual return to baseline by 90 min after termination of stressor	[a]	GR antagonism in the LV prevented increase
Butts and Phillips (2013)	SD rat	15 min	Acute	15	225 %	Increase during stress, reduced upon termination and back to baseline by 30 min later	[a]	GR antagonists prevented increase

[a] Dopamine did not return to baseline prior to stressor termination and so cannot be assessed

mPFC medial prefrontal cortex, *DA* dopamine, *BL* baseline, *SD* Sprague–Dawley, *CCE* chronic cold exposure, *CMS* chronic mild stress, *GR* glucocorticoid receptor, *LV* lateral ventricle, *n/a* not available

not alter extracellular dopamine in either brain region, although these stressors work synergistically to increase dopamine when administered concurrently (Merali et al. 1997).

One potentially important distinction is that all the above-mentioned stressors involve direct physical tactile contact/stimulation of the animal. However, stressors that do not involve direct contact with the animals' body can also elicit strong increases in extracellular dopamine in both the NAc and mPFC. The "psychological" stress of observing and smelling nine other rats receiving severe (3.0 mA) footshocks elicits a significant increase in extracellular dopamine in the NAc shell, but not core (Wu et al. 1999), one of the only studies to examine the difference in responsivity to stress between these subregions of the NAc. Additionally, presentation of a predator (fox) odor produces a gradual increase to 205 % baseline levels in extracellular dopamine in the mPFC (Wu et al. 2003).

It is possible that these findings showing stress-induced elevations in extracellular NAc and mPFC dopamine are in line with a hypothesis that VTA dopamine neurons primarily subserve reward-related functions as opposed to stress-related functions. The removal of a stressor or aversive stimulus is negative reinforcement and can strengthen subsequent associated behaviors (Thorndike et al. 1932). Considerable behavioral evidence has demonstrated that the termination of a stressor or aversive stimulus can serve as a reward (e.g., Navratilova et al. 2012; Tanimoto et al. 2004). Thus, it could be expected that rather than stress activating these dopaminergic neurons, it is actually the offset of stress that excites VTA dopamine neurons, resulting in the observed extracellular dopamine increases in VTA projection sites. Indeed, approximately half of the VTA dopamine neurons inhibited by footshock also show excitation at the termination of the aversive stimulation (Brischoux et al. 2009).

Some microdialysis studies are in support of this explanation. Although restraint stress produces a sustained elevation

Table 7 Effect of tail shock stress on extracellular dopamine in the mPFC

Reference	Species	Stressor parameters	Stressor pattern	Sample length (min)	Max DA (%BL)	Time course of DA efflux	Increase at termination?	Additional findings
Abercrombie et al. (1989)	SD rat	1.0-mA pulses for 1 s every 10 s for duration of 1 min, repeated every 5 min for 30 min	Acute	20	195 %	Immediate increase, peaking in 2nd half of stressor immediately returned to baseline after termination	No	
Gresch et al. (1994)	SD rat	1.0-mA pulses for 1 s every 10 s for duration of 45 s, repeated every 5 min for 30 min	acute, with 17–28-day prior chronic cold exposure	30	150 %, 271 %	Immediate increases in naïve (150 % max) and CCE (271 %), sustained for 60 min after termination	[a]	
Bland et al. (2003)	SD rat	1.0 mA, 100 trials, ITI avg 60 s, terminated by escapable shock (ES) rat turning wheel	Acute, escapable (ES) or inescapable (IS)	20	150 %, 275 %	ES showed initial immediate increase to 150 %, returning to baseline after the first sample. IS increased to 150 % initially, peaking at 275 % subsequently and gradually returned to baseline by 200 min after initiation of stress	No	
Murphy et al. (2003)	SD rat	1.0-mA constant pulse for 1 s every 10 s for duration of 45 s, repeated every 5 min for 30 min	Acute, with prior 14–20-day chronic cold exposure	15	183 %, 258 %	Naïve rats immediately increased mPFC DA (183 %), returning to baseline immediately upon shock termination. Prior CCE rats: immediate increase to 258 %, while also immediately returning to baseline on termination	No	ICV CRF antagonist did not alter evoked dopamine increase, but attenuated CRF-induced dopamine increase

[a] Dopamine did not return to baseline prior to stressor termination and so cannot be assessed

mPFC medial prefrontal cortex, *DA* dopamine, *BL* baseline, *SD* Sprague–Dawley, *CCE* chronic cold exposure, *ES* escapable shock, *CRF* corticotropin releasing factor

in extracellular dopamine in both the NAc and mPFC (Tables 1 and 2), when restraint or immobilization is prolonged until dopamine levels return to baseline, most have shown that there is a strong, rapid increase in extracellular dopamine levels again upon release (Imperato et al. 1992; Imperato et al. 1991; Jackson and Moghaddam 2004; Lillrank et al. 1999; Pozzi et al. 2002; Puglisi-Allegra et al. 1991; Swanson et al. 2004). However, it is difficult to evaluate a dopamine response to the termination of a stressor, as most other types of stress studied (e.g., footshock and tail pinch) are much shorter in duration, rarely spanning greater than two microdialysis samples, and do not show a return to baseline prior to the termination of the stressor. Therefore, it cannot be concluded that any significant increases after termination of the stressor are due to negative reinforcement as opposed to carryover from the aversive experience. Regardless, this hypothesis that the dopamine increase is due to negative reinforcement as opposed to stress itself cannot explain the sustained dopaminergic increases observed in microdialysis studies where the stressors or aversive stimuli outlast the sampling time.

Thus, while the temporal resolution and correlational nature of these microdialysis experiments could not conclusively prove that VTA dopamine neurons are excited by stress as opposed to the removal of a stressor, the magnitude and duration of dopaminergic increases in these target areas indicate a likely effect on VTA firing in response to stress. Overall, as summarized in Fig. 3, most stressors elicit an increase in extracellular dopamine in VTA projection targets, with the most potent stressors eliciting the greatest changes from baseline. However, with milder stressors, there seems to be a greater increase in mPFC dopamine compared with NAc dopamine, indicating a possible lower threshold of stimulation or alternative function for mPFC projecting dopamine neurons. Alternatively, mPFC projecting dopamine neurons may be less sensitive to different types of stressors.

Table 8 Effect of other stressors on extracellular dopamine in the NAc

Reference	Species	Stressor parameters	Stressor pattern	Sample length (min)	Max DA (%BL)	Time course of DA efflux	Increase at termination?	Additional findings
Azzi et al. (1998)	Wistar rat	10-min forced swim	Acute	20	n/a	No effect in NAcSh, although the sample was twice as long as the stressor	No	
Wu et al. (1999)	Wistar rat	"Psychological"-rat in center compartment of a 9-compartment chamber divided by plexiglass, all other compartments received shocks at 3.0 mA for 5 s in 30-s intervals for 20 min	Acute	20	155 %	Significantly increased during stress, remained elevated after termination, returned to baseline 40 min after termination	[a]	No effect in NAc core
Merali et al. (1997)	SD rat	Airpuff and/or cytokine (IL-8) injection	Acute	30	n/a	No effects	n/a	
Feenstra et al. (1998)	Wistar rat	16-min handling	Acute	15	130 %	Peaks during handling, sustained 15 min after termination	[a]	local inhibition (reverse dialysis) of ionotropic glutamate receptors did not affect handling induced corticosterone, dopamine, or noradrenaline release, nor did an mGluR antagonist or GABAB agonist
IInglis and Moghadda-m (1999)	SD rat	20-min handling	Acute	20	150 %	Not significantly elevated during handling (125 %), but significant increase at release (150 %), which was sustained for 40 min	Yes	
Cenci et al. (1992)	SD rat, female	15-min handling	Acute	15	n/a	No effect	n/a	
Tidey and Miczek (1996)	Long Evans rat	Social threat; 40 min in aggressors homecage without aggressor, 60 min with aggressor behind screen, 40 min again with no aggressor	Acute, with prior history of 4 social defeats	20	160 %	Initial response to cage without aggressor (137 %), with peak in response to introduction of aggressor (160 %), returned to 130 % when aggressor was removed, and increased again (148 %) when returned to homecage	Yes, not seen in controls	
Tidey and Miczek (1997)	Long Evans rat	Social threat; 40 min in aggressors homecage without aggressor, 60 min with aggressor behind screen, 40 min again with no aggressor	Acute, with prior history of 4 social defeats	20	143 %	Initial response to aggressor's homecage (133.5 %), with peak in response to resident aggressor (143 %). Gradual return to baseline, but did not measure return to homecage	Did not measure	Faster acquisition of cocaine self-administration compared to rats with no history of defeat
Jezierski et al. (2007)	juvenile degu	60-min isolation, with or without 3 weeks daily maternal separation	Acute	20	169 %, 150 %	Larger increase in control compared to early separation group, both groups returned to baseline immediately upon reunion	No	Chronic methylphenidate cross-sensitizes

[a] Dopamine did not return to baseline prior to stressor termination and so cannot be assessed

NAc nucleus accumbens, *DA* dopamine, *BL* baseline, *SD* Sprague–Dawley, *n/a* not available

Table 9 Effect of other stressors on extracellular dopamine in the mPFC

Reference	Species	Stressor parameters	Stressor pattern	Sample length (min)	Max DA (%BL)	Time course of DA efflux	Increase at termination?	Additional findings
Merali et al. (1997)	SD rat	Airpuff and/or cytokine (IL-8) injection	acute	30	n/a	No effect	n/a	
Azzi et al. (1998)	Wistar rat	10-min forced swim	acute	20	n/a	Marginal increase, sustained at least 200 min, but does not report baseline	[a]	Repeated administration of neurotensin antagonist has no effect
Jordan et al. (1994)	SD rat	8-min forced swim, repeated 24 h later	repeated once	30	n/a, 441 %	No effect on day 1, but second day significant increase, persisting for 60 min after termination	[a]	
Petty et al. (1997)	SD rat	8-min forced swim, repeated 24 h later	repeated once	30	n/a, 200 %	Day 1: no effect on dopamine. Day 2: increased to 200 % during stress, peaked after termination at approximately 300 %, sustained for 90 min	[a]	Flumazenil increased stress response on day 1; diazepam attenuated stress response on day 2
Cenci et al. (1992)	SD rat, female	15-min handling	acute	15	n/a	No effect	n/a	
Enrico et al. (1998)	Wistar rat	15-min handling	acute	15	225 %	150 % during stress, increased to maximal 225 % after release, gradually decreased back to baseline by 90 min after termination	[a]	Intra-VTA baclofen, CPP, AP5, CNQX suppressed handling induced increases, while intra-VTA muscimol, atropine, mecamylamine, and +−HA-966 did not
Feenstra et al. (1998)	Wistar rat	16-min handling	acute	15	300 %	Peaked during handling, gradual return to baseline by 60 min after release	[a]	Local inhibition (reverse dialysis) of ionotropic glutamate receptors did not affect handling induced corticosterone, dopamine, or noradrenaline release, nor did an mGluR antagonist or GABAB agonist
Takahata and Moghaddam (1998)	SD rat	20-min handling	acute	20	150 %	Increased during handling, immediate return to baseline after termination	No	Blockade of AMPA and NMDA receptors in the VTA during handling reduced dopaminergic response
Inglis and Moghaddam (1999)	SD rat	20-min handling	acute	20	150 %	Immediate increase, sustained 20 min after release	[a]	
Del Arco and Mora (2001)	Wistar rat	40-min handling	acute	20	200 %	Increase sustained during handling, decreased slightly at termination and return to baseline by 20 min after release	[a]	No effects on GABA or glutamate in mPFC
Del Arco et al. (2001)	Wistar rat	40-min handling	acute	20	189 %	Increased during handling, immediate return to baseline after termination	No	
Marsteller et al. (2002)	SD rat	15-min handling	acute	15	155 %	Increase during handling, peak after cessation, rapid return to baseline	[a]	
Del Arco et al. (2007)	Wistar rat	40-min handling	acute	20	150 %	Increase during handling, remained elevated at release, return to	[a]	No effects of prior environmental enrichment

Table 9 (continued)

Reference	Species	Stressor parameters	Stressor pattern	Sample length (min)	Max DA (%BL)	Time course of DA efflux	Increase at termination?	Additional findings
						baseline by 40 min after termination		
Kawahara et al. (1999)	Wistar rat	10-min handling	acute	15	175 %	Increased during handling, slow return to baseline	[a]	Intravenous infusion of sodium nitroprusside (induces hypotension) also potently increases mPFC DA
Pehek et al. (2006)	SD rat	20-min handling	acute	20	182 %	Increased during handling, immediate return to baseline	No	
Tidey and Miczek (1996)	Long Evans rat	Social threat; 40 min in aggressor homecage without aggressor, 60 min with aggressor behind screen, 40 min again with no aggressor	acute, with prior history of 4 social defeats	20	160 %	Initial response to cage without aggressor (136 %), with peak in response to introduction of aggressor (162 %), returned to 130 % when aggressor was removed, and increased again (148 %) when returned to homecage	Yes, not seen in controls	
Watt et al. (2014)	SD rat	Adolescent social defeat; 20-min exposure to resident	acute, with three prior social defeats	20	150 %	Increased during encounter, slowly returned to baseline by 60 min after termination	[a]	
Jezierski et al. (2007)	juvenile degu	60-min isolation, with or without 3 weeks daily maternal separation	acute	20	171 %, 146 %	Larger increase in control compared to early separation group, both groups returned to baseline immediately upon reunion	No	Chronic methylphenidate cross-sensitizes
Wu et al. (2003)	SD rat	Predator odor (fox) for 20 min	acute	20	205 %	Gradual increase in dopamine that was maximal 120 min after beginning of odor presentation	[a]	

[a] Dopamine did not return to baseline prior to stressor termination and so cannot be assessed

mPFC medial prefrontal cortex, *DA* dopamine, *BL* baseline, *SD* Sprague–Dawley, *VTA* ventral tegmental area, *n/a* not available

Electrophysiological evidence

Initially, extracellular increases in dopamine concentration in VTA projection targets were difficult to reconcile, as most studies had shown a suppression of VTA dopamine neuronal firing during stress or aversive stimulus presentation (Guarraci and Kapp 1999; Mantz et al. 1989; Mirenowicz and Schultz 1996; Schultz and Romo 1987; Ungless et al. 2004). However, recent evidence demonstrates that there is in fact a subset of dopamine neurons within the VTA that are rapidly and potently excited by stressful, aversive stimuli. Single unit recordings in awake rats showed that both firing rate and burst firing are increased in putative VTA dopamine neurons during restraint stress (Anstrom and Woodward 2005), while multi-unit recording showed similar increases in burst firing, but not firing rate, during social defeat stress (Anstrom et al. 2009). Burst firing is thought to play an important functional role in dopamine release, as frequencies may overwhelm the dopamine transporter, causing supralinear increases in extracellular dopamine concentration (Gonon 1988).

As described in section Heterogeneity in electrophysiological profile, most in vivo electrophysiological studies have focused on the dorsolateral VTA dopamine neurons using classic criteria, particularly large *Ih* current. When examining ventromedial VTA dopamine neurons, which were characterized by smaller *Ih* currents, Brischoux and colleagues (2009) found that there was a subset of neurons rapidly and strongly excited by stress (Fig. 4). Similarly, others have found increased activity in these "non-conventional" VTA dopamine neurons in response to aversive stimulus presentation (Cohen et al. 2012; Zweifel et al. 2011). It

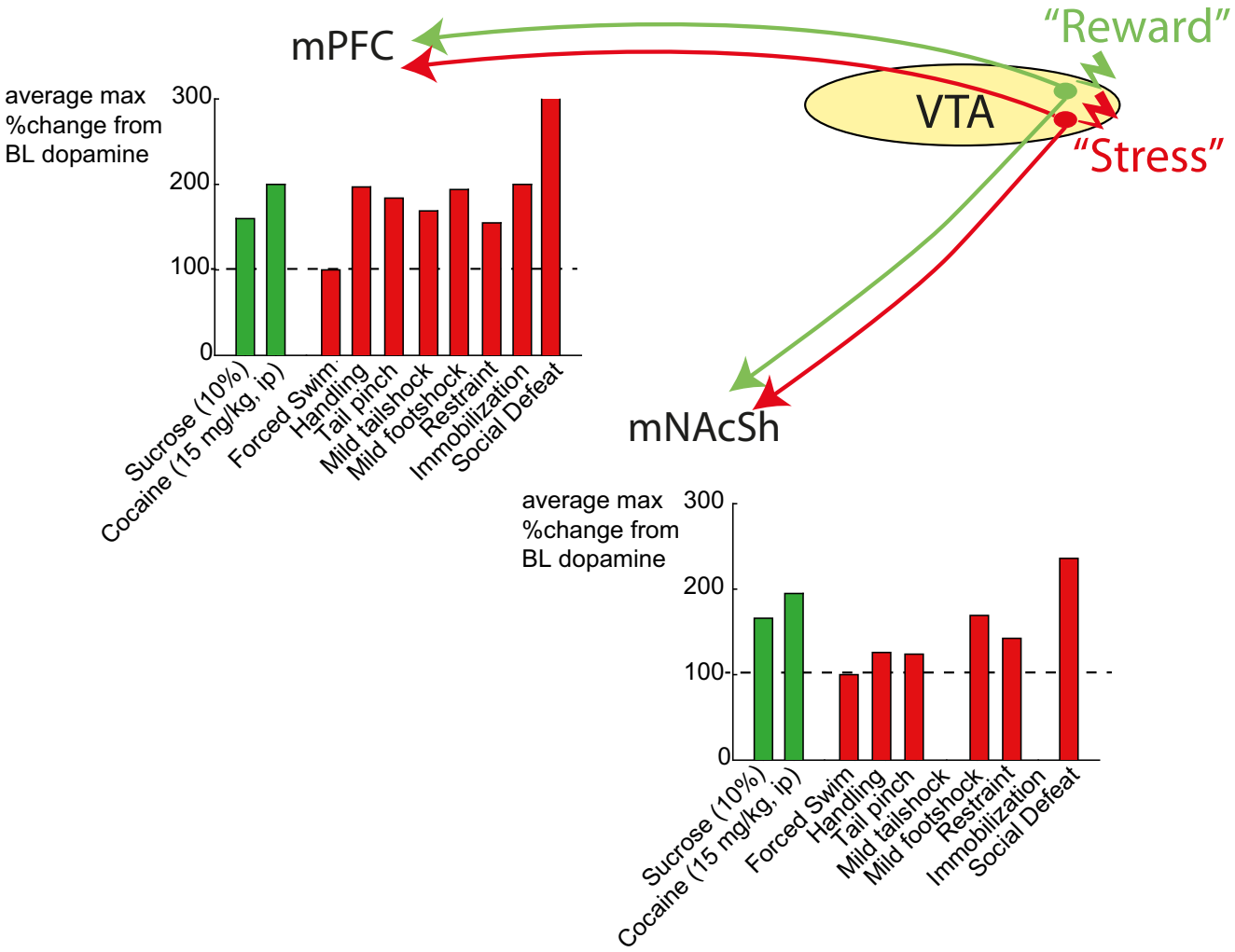

Fig. 3 Reward and stress activate VTA dopamine neurons, increasing extracellular dopamine in the mPFC and NAcSh. Both rewarding and stressful stimuli induce dopaminergic increases in ventral tegmental area (VTA) projection targets, namely, the medial prefrontal cortex (mPFC) and nucleus accumbens shell (NAcSh), to a similar degree. Average maximal percent change from baseline dopamine is representative of papers presented in Tables 1, 2, 3, 4, 5, 6, 7, 8, and 9

is highly likely that a subpopulation of dopamine neurons responsive to aversive or stressful stimuli have been overlooked in prior work due to sampling bias and mischaracterization of VTA dopamine neurons (Brischoux et al. 2009; Ungless et al. 2010; Ungless and Grace 2012). In light of this growing evidence, it has been proposed that there are at least two subpopulations of VTA dopamine neurons: one group encoding reward-prediction error that is suppressed by aversive stimulation, and a second group, with atypical *Ih* and high baseline burst firing, that is phasically stimulated by aversive stimuli (Ungless et al. 2010).

Evidence for neuroadaptations on VTA dopamine neurons

Exposure to a single acute stressor can also promote long-lasting neuroplastic changes in VTA dopamine neurons in a manner similar to exposure to drugs of abuse (Dong et al. 2004; Graziane et al. 2013; Niehaus et al. 2010; Saal et al. 2003). Acute stress induces long-term potentiation (LTP) at glutamatergic synapses onto VTA dopamine neurons, while concurrently blocking the formation of LTP at GABAergic synapses (Graziane et al. 2013; Niehaus et al. 2010). During induction of LTP at glutamatergic synapses, new AMPA receptors are inserted, increasing the AMPA/NMDA ratio and increasing later excitability of the postsynaptic neuron (Malinow and Malenka 2002). This alteration in the AMPA/NMDA ratio enhances calcium permeability and changes calcium dynamics in the synapse, such that subthreshold stimulation can induce robust LTP (Polter and Kauer 2014). Acute exposure to stress increases this ratio of AMPA to NMDA receptors within excitatory synapses on VTA dopamine neurons (Dong et al. 2004; Graziane et al. 2013; Saal et al. 2003). However, consistent with the theme of importance of

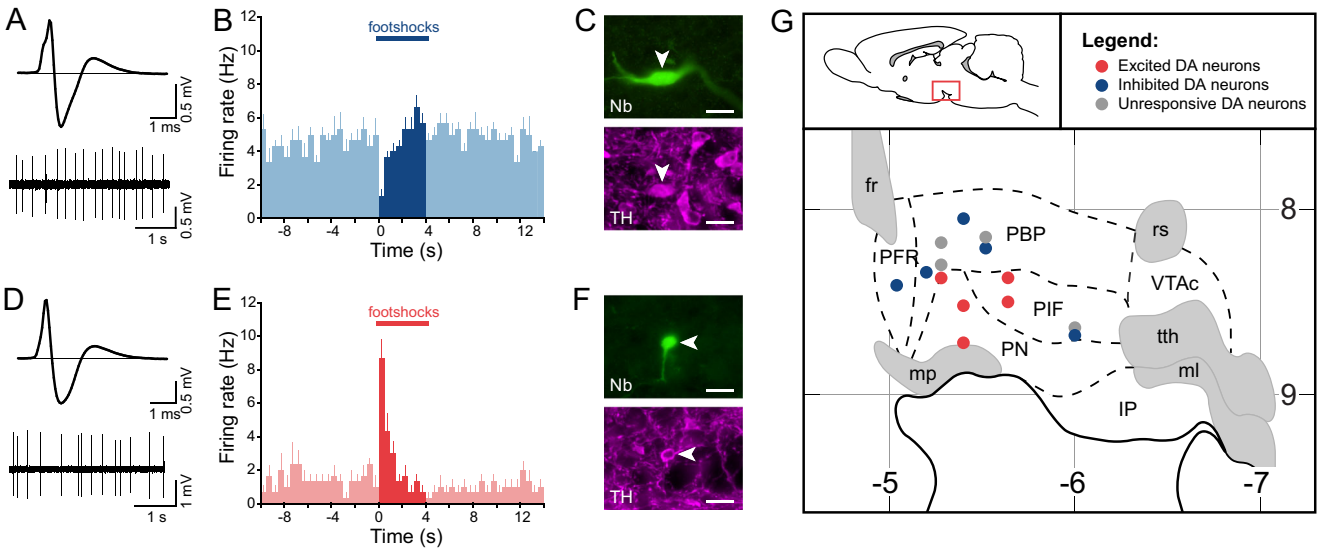

Fig. 4 Dorsal VTA dopamine neurons are inhibited by noxious stimuli, whereas ventral VTA dopamine neurons are excited. **a** Averaged extracellular waveform and baseline firing activity from a recorded neuron. **b**, **c** This neuron showed an inhibitory response to footshocks (**b**) (peristimulus time histogram averaged across six footshocks; mean+SEM; 500-ms bins) and was immunohistochemically identified as dopaminergic (**c**) (Nb indicates neurobiotin). **d**–**f** In contrast, a second neuron with a similar averaged extracellular waveform and baseline firing rate (**d**) showed an excitatory response to footshocks (**e**), but was also immunohistochemically identified as dopaminergic (**f**). (*Scale bars*: 20 μm.) **g** A parasagittal schematic view of the VTA (lateral, 0.6 mm) showing the distribution of individual dopamine neurons and their responses to footshocks and showing a clear anatomical segregation of functional subgroups (horizontal numbers are distance from bregma in millimeters; vertical numbers are depth in millimeters). fr, fasciculus retroflexus; IP, interpeduncular nucleus; ml, medial lemniscus; mp, mammillary peduncle; PBP, parabrachial pigmented nucleus; PFR, parafasciculus retroflexus area; PIF, parainterfascicular nucleus; PN, paranigral nucleus; rs, rubrospinal tract; tth, trigeminothalamic tract; VTAc, ventral tegmental area caudal. Reprinted with permission from Brischoux et al. (2009) in *PNAS*

VTA heterogeneity, distinct regional differences in AMPA/NMDA ratio alterations within the VTA have been observed after acute stress exposure. Injection of formalin into the hindpaw, an intense noxious stimulus, results in a significant increase in the AMPA/NMDA ratio in medial VTA dopamine neurons projecting to the mPFC, whereas VTA dopamine neurons projecting to the NAc shell do not exhibit such alterations (Lammel et al. 2011). These increases in AMPA/NMDA ratio are present within 2 h of stress and have been observed for at least 24 h (Daftary et al. 2009). Furthermore, intra-VTA antagonism of both AMPA and NMDA receptors prevents tail pinch–induced dopamine efflux in the mPFC, although the NAc has not been examined (Butts and Phillips 2013).

Recent evidence also demonstrates that acute exposure to stress can block the induction of LTP at $GABA_A$ synapses on VTA dopamine neurons (Graziane et al. 2013; Niehaus et al. 2010). VTA dopamine neurons are relatively depolarized at baseline, and thus typically at or very close to action potential threshold (Graziane et al. 2013; Johnson and North 1992). This loss of LTP at inhibitory synapses on VTA dopamine neurons may represent the removal of a brake on the system, which combined with the induction of LTP at excitatory synapses can lead to increased responsivity of VTA dopamine neurons to future stimulation, whether by additional stressors or rewards such as drugs of abuse.

Effects of repeated and chronic stress on VTA dopamine neuron activity

Activation of VTA dopamine neurons during acute stress exposure and subsequent neuroadaptations may result in altered VTA dopamine response to later stimulation. The effects of repeated or chronic stress on VTA dopamine neurons have remained largely unstudied by electrophysiological measures, as electrophysiological evidence for a subset of VTA dopamine neuron activation by stress has only recently emerged. However, a few in vivo microdialysis studies indicate that repeated exposure to stress might indeed alter dopaminergic release in VTA projection targets, particularly the NAc and mPFC. Importantly, repeated stress exposure can affect both tonic (basal levels) and phasic (release in response to stimulation) dopamine in the NAc and mPFC.

The schedule, intensity, and nature of stressors or aversive stimuli again have differential effects on extracellular NAc and mPFC dopamine, related to altered VTA dopamine neuron activity. For example, repeated intermittent exposure to social defeat stress increases dopaminergic tone in the NAc (Miczek et al. 2011), while chronic social defeat reduces overall dopaminergic tone in both males and females (Miczek et al. 2011; Shimamoto et al. 2011). Chronic, inescapable restraint stress, a relatively severe stressor, also decreases dopamine

tone in the NAc (Mangiavacchi et al. 2001), while other animal models used to study symptoms of depression such as chronic cold and chronic mild stress have no effect on basal dopaminergic tone in the NAc, striatum, or mPFC (Di Chiara et al. 1999; Gresch et al. 1994). Both chronic restraint and repeated social defeat stress increase both spontaneous and burst firing of VTA dopamine neurons (Anstrom et al. 2009; Anstrom and Woodward 2005; Cao et al. 2010; Krishnan et al. 2007). Notably, studies investigating individual differences in responses to chronic social defeat have found that these effects on VTA firing are only observed in susceptible mice that exhibit behavioral signs of anhedonia (Cao et al. 2010; Feder et al. 2009; Krishnan et al. 2007). Furthermore, these effects are long-lasting, still observed 3 weeks after stress termination (Razzoli et al. 2011).

In addition to altered tonic dopamine in VTA projection targets, the phasic dopamine response in the NAc and mPFC to subsequent stressors is also altered. While daily restraint stress for 6 consecutive days results in a habituation of the extracellular dopamine response in the NAc across time, when restraint is again repeated after 72 h, the extracellular dopamine phasic response in the NAc is equivalent to the response on the first day (Imperato et al. 1992; Imperato et al. 1993). Repeated footshock stress (Young 2004) and intermittent social defeat stress (Holly et al. 2015), on the other hand, do not show such habituation in the phasic extracellular NAc dopamine response, while a sensitized response is observed after the much milder stresses of repeated tail pinch (Naef et al. 2013) or forced swim (Jordan et al. 1994; Petty et al. 1997).

In addition to altered responses to repeated presentations of the same stressor, a history of repeated stress can also alter the subsequent phasic extracellular dopamine response to a different stressor. Prior history of chronic variable stress results in a significantly greater phasic extracellular dopamine response in the mPFC in response to restraint stress (Cuadra et al. 2001; Cuadra et al. 1999), as well as both the NAc and mPFC during tail pinch stress (Di Chiara et al. 1999) compared to previously non-stressed controls. Continuous chronic cold exposure, another model of repeated stress shown to elicit anhedonic-like responses in rodents, also produces greater mPFC phasic extracellular dopamine responses to tail pinch (Finlay et al. 1995) and tail shock (Gresch et al. 1994; Murphy et al. 2003). A similar sensitized effect of extracellular NAc dopamine is observed in animals with a history of isolation rearing in response to footshock stress (Fulford and Marsden 1998), and history of prior social defeat stress results in greater NAc and mPFC response to social threat compared to previously non-stressed controls (Tidey and Miczek 1996, 1997; Watt et al. 2014). When repeated footshock stress is paired with a conditioned stimulus (CS), an augmented response is observed in both the NAc and mPFC, with the CS alone significantly elevating extracellular dopamine above baseline (Feenstra et al. 2001; Young 2004; Young et al. 1993).

Overall, while the effects of repeated stress on VTA dopamine neuron activity and related tonic and phasic dopamine levels in the NAc and mPFC have received only limited attention, current evidence points to a clear effect of repeated stress on subsequent tonic dopamine activity as well as subsequent response to both identical and different stressors. As with the effects of acute stress, the nature, intensity, and schedule of repeated stress are critical, such that mild or intermittent stressors may potentiate basal VTA dopamine neuron activity and more severe or chronic uncontrollable stressors may reduce basal VTA dopamine activity, but the response to later stressors of a different nature is generally cross-sensitized.

Conclusions and future perspectives

Two critical themes regarding the role of VTA dopamine neurons in response to stress have emerged within this review: (i) The heterogeneous structure of the VTA may be the basis for divergent functions in aversion and reward, and (ii) the nature, schedule, and intensity of the stressor matter. Recent research demonstrates that there may be at least two distinct types of VTA dopamine neurons mediating different behavioral functions, namely, reward and aversion. Anatomical, neurochemical, and electrophysiological data reveal a subset of dopamine neurons in the ventral posteromedial VTA that have previously been ignored and are rapidly and potently excited by stress. Future research should be driven to determine the specific afferent and efferent connections of this particular subtype.

The nature of stressors and aversive stimuli are also crucial to the interpretation of both microdialysis and electrophysiology results. A general tendency of past research has been to extrapolate findings with one type of stressor to a general response to all types of stressors. However, as reviewed here, it is clear that the nature, intensity, and schedule of repeated stress can have vastly different effects on dopamine release in VTA projection targets. Notably, the comparatively mild, inescapable stress of chronic cold induces a pronounced reduction in VTA dopamine neuron activity, whereas more severe inescapable stress such as acute restraint can increase this neuronal activity (Moore et al. 2001; Valenti et al. 2012). Of note, chronic stressors generally used as animal models of depression, such as chronic cold exposure or chronic mild stress, generally tend to blunt subsequent tonic dopaminergic activity, while more severe acute or intermittent stressors, such as those typically associated with anxiety or heightened vulnerability to subsequent addictive-like behaviors, tend to augment tonic dopaminergic activity. However, even within each so-called class of stressors, different stimuli can still promote profoundly different effects on not only tonic and phasic dopamine but also behavior.

Importantly, the emerging evidence reviewed here suggests that a small subpopulation of dopamine neurons in the VTA is

responsive to stressful and aversive stimuli. Molecularly characterizing this specific subset of VTA dopamine neurons may give rise to the use of targeted techniques to elucidate direct monosynaptic afferents/efferents as well as directly manipulate these neurons through optogenetics, or designer receptors exclusively activated by designer drugs (DREADDs). Understanding which dopamine neurons are activated by stress, the neural mechanisms driving the activation, and where these neurons project to will provide valuable insight into how stress can promote psychiatric disorders associated with the limbic system, such as addiction and depression. This information can then provide new, improved avenues for therapeutic intervention when stress shifts from an adaptive to a maladaptive response.

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