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REVIEWS

Sensitivity of the Dopamine System to Stress

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Abstract

Pathological conditions such as post traumatic stress disorder (PTSD) and anxiety disorders may result from the inability to properly respond to stress. The extended amygdala is highly involved in the stress response and receives substantial dopaminergic innervation. The dopamine (DA) system is sensitive to stress, but its role in the stress response is not fully understood. Dopamine concentration and metabolism increase within target regions after exposure to stressors. The firing of DA neurons is also altered after stress exposure. The DA system receives norepinephrine (NE) inputs that may, in part, mediate some of these actions. Indeed, NE modulates the firing of DA neurons through the activation of α1 and α2 adrenergic receptors (ARs). This review highlights the evidence of DA's involvement in stress and the potential role NE plays in mediating these actions, with a focus on the dopamine projections to the extended amygdala.

Keywords

Stress
Anxiety
Dopamine
Norepinephrine
Ventral tegmental area
Extended amygdala,
Burst firing

Introduction

Chronic stress or alterations in the appropriate physiological response to stress may lead to pathological conditions such as anxiety, panic disorders, post-traumatic stress disorder (PTSD), or perhaps drug abuse. The extended amygdala, which consists of the bed nucleus of the stria terminalis (BNST), the central nucleus of the amygdala (CeA), and the nucleus accumbens (NAc) shell, has been shown to play an important role in stress, anxiety, and addiction-related behaviors[1-3]. For example, inhibition of GABA synthesis in the BNST leads to an increase in anxiety-like behavior in rats[4]. Stress-related information is provided to the extended amygdala by a variety of afferents, including catecholamines arising from NE and DA centers. Many stressors increase the firing of NE neurons and increase NE turnover in target regions, such as the BNST[5-7]. Although there is a large literature focused on the role of NE in stress, this review will focus on the actions of stress on the DA system. Dopamine is classically regarded as the reward neurotransmitter, however, the midbrain DA system has been recognized to be sensitive to stress even though this impact is not well understood. Delineating the ways in which stress modulates the DA system will allow a better understanding of the mechanisms mediating the interaction of stress and reward.

Anatomy of dopaminergic innervation of the extended amygdala

It has long been known that the DA neurons that project to the extended amygdala arise from the ventral tegmental area (VTA), substantia nigra pars compacta (SNc), and retrorubral nucleus (RR)[8-13]. The population of DA neurons projecting to each region of the extended amygdala was quantitatively determined using retrograde tracers and tyrosine hydroxylase (TH) immunohistochemistry[14]. The NAc shell receives approximately 80% of its DA projections from the VTA-A10[a] group, with the highest percentage arising from the parabrachial pigmented (PBP) and caudal linear (CLi) nuclei. The CeA and BNST have very similar distributions with approximately 40% of the DA projections coming from the VTA-A10 group (majority from PBP and CLi) and approximately 50% from the A10dc area, which consists of the periaqueductal gray (PAG) and dorsal raphe (DR). The majority of studies that investigate the role of DA neurons in stress and addiction primarily focus on the parabrachial pigmented nucleus of the lateral VTA. Very few studies examine the midline DA neurons of the rostral linear nucleus (RLi), CLi, PAG and DR regions. Given the diverse projection targets of these regions, new insights may be gained from studies focused on the actions of these mid-

a. **Dopaminergic cell groups:** The DA population has been divided into distinct cell groups termed A8-A14. A8 refers to the RR nucleus, A9 is primarily the SNc, and A10 is the VTA. The A10-VTA can be divided into four distinct nuclei: parabrachial pigmented, paranigral, interfascicular, and caudal linear nuclei. The rostral linear nucleus was later added to the A10 group. The DA neurons of the PAG and DR are considered to be a dorsocaudal extent of A10 termed the A10dc. See Hasue and Shammah-Lagnado 2002 for further explanation of the DA cell groups.

line dopamine populations.

Anatomy of noradrenergic innervation of the dopamine system

The role of NE in stress has been widely studied[5-7, 15, 16]. Norepinephrine arises from the locus coeruleus (termed A4 and A6 areas), ventral medulla (A1, A5 and A7 areas), and the dorsomedial medulla (A2 area). The locus coeruleus (LC) has a broad projection field, and NE arising from the LC has been shown to play roles in arousal and cognitive performance[17, 18]. The non-LC NE neurons are located in brainstem, homeostatic centers and have been shown to be involved in a variety of processes. For example, A1 neurons control the release of vasopressin, A2 neurons are involved in regulation of food intake, and A5 neurons regulate the respiratory rhythm generator of the rostral ventrolateral medulla[19-21]. It has long been known that the LC projects to the VTA[22-25]. Recently, it was determined that a large number of non-LC noradrenergic projections innervate DA regions. Using dopamine beta hydroxylase (DBH) immunohistochemistry and anatomical tracing studies, Mejías-Aponte *et al.* found that the midline areas of RLi and CLi receive noradrenergic innervation from A1, A5 and LC[26]. The LC and A5 innervate the medial VTA while the lateral VTA receives innervation from A1, A2, A5 and LC[26]. There is also a noradrenergic input from the LC to the PAG, near the A10dc DA population[27]. These abundant NE innervations make the midbrain DA neurons prime candidates to undergo modulation due to stress. Furthermore, the varying noradrenergic inputs combined with distinct projection targets of diverse DA neuron populations indicate a possible differential sensitivity to stress.

Sensitivity of the dopamine system to stress

Extensive studies have explored the involvement of NE in stress. Furthermore, there is also evidence that DA is important for stress-related behaviors, particularly in the extended amygdala and prefrontal cortex. Acute intermittent tail shock increases extracellular DA concentration in the striatum, NAc, and medial prefrontal cortex (mPFC) with the mPFC showing the largest increase above basal levels[28]. An increase in DA concentration in rats exposed to foot shock stress occurs in the NAc shell[29, 30]. Also, rats who are predisposed to psychostimulant self administration undergo a larger and longer-lasting increase in DA concentration in the NAc, following tail pinch stress, as compared to those who are not predisposed[31]. Furthermore, acute immobilization and restraint stressors increase DA metabolism in the rat mPFC and the NAc shell while exposure to the predator odor, 2,5-dihydro-2,4,5-trimethylthia-zoline (TMT), increases DA metabolism in only the mPFC[32-34]. In summary, different types of acute stressors increase DA concentration and metabolism in numerous brain regions.

There are also actions of DA following stressors in other regions of the extended amygdala. The metabolism of DA increases within the CeA and BNST following foot shock stress in rats[35]. Interestingly, in a study done by Cecchi *et al.,* one session of immobilization stress significantly increases the level of NE, but not DA, in the lateral BNST of rats[7]. However, these rats were singly housed for 5-7 days prior to the immobilization stress and there is evidence that prolonged social isolation in mice leads to an increase in anxiety-like behavior[36]. Also, following chronic stress paradigms such as six days of restraint stress or three weeks of restraint stress combined with unavoidable tail shock, the concentration of DA and its metabolites decreases in the NAc shell[37, 38]. Therefore, the rats in the Cecchi *et al.* study may be undergoing a stress paradigm similar to chronic stress in which an increase in the level of DA in the BNST would not be expected. Further studies are needed to elucidate any changes in DA concentration or metabolism in the BNST and CeA that arise as a result of acute or chronic stress exposure.

Stress may also lead to an increase in *c-fos* expression in animals. In the CeA of the rat, there is an increase in Fos immunoreactivity following acute immobilization stress[39]. This CeA Fos staining is enriched in regions that overlap with TH positive terminals[40]. In rats, exposure to TMT and mild foot shock also leads to an increase in Fos immunoreactivity among DA neurons of the A10-VTA, but not in the A9-SNc region[41]. Furthermore, Deutch and colleagues found that restraint stress increases Fos staining within the VTA of rats[33]. This increase varies by VTA subregions and is highest in the PBP and CLi. The increase in Fos expression is partially blocked with treatment of diazepam prior to administration of the stressor. Interestingly, treatment with the anxiogenic β-carboline, FG 7142, increases Fos expression to a greater extent than restraint stress in the CLi and to a lesser extent in the PBP[33]. This evidence suggests that the CLi may play a larger role in stress and anxiogenic behaviors than other VTA nuclei. Through the use of retrograde tracers, Deutch and colleagues determined that the majority of double-labeled Fos and TH neurons project to the mPFC, with few projecting to the NAc. Additionally, the CLi DA neurons heavily project to the BNST and CeA, but this study did not determine whether the Fos-labeled cells project to these regions of the extended amygdala. As such, more work needs to be done to determine whether or

not the DA neurons that project to the extended amygdala are activated by stress exposure. Such work is important as activation of immediate early genes, such as *c-fos*, represents metabolic activation or increase in neuronal, activity, which may occur due to exposure to stressor. Therefore, based upon the changes in Fos expression and DA concentration in target regions as described above, alterations in firing of DA neurons after stress exposure might be expected.

Exposure to stressors modulates firing in dopamine neurons

The firing of DA neurons is characterized by a low frequency tonic or pacemaker firing that is interspersed with phasic bursting activity. Spontaneous pacemaker firing is independent of afferent input, while bursting activity is stimulated by NMDA receptor activation[42-46]. Bursting activity leads to a larger increase in synaptic DA than regular firing and is thought to occur during the presentation of reward or salient cues[45, 47-49]. There is some evidence that the firing of DA neurons is inhibited by aversive stimuli, such as foot shock, in anesthetized rats[50]. However, there are studies in which firing of putative DA neurons is enhanced with stress. For example, one session of restraint stress enhances firing in VTA DA neurons in awake rats[51]. This increase is only in cells that have a high level of basal bursting activity as compared to those with a regular firing pattern. Also, stress increases the amount of spikes seen within bursts, rather than the amount of bursts themselves. This increase in activity persists for at least twenty-four (24) hours. A second session of restraint stress, on the subsequent day, does not further increase firing activity. Additionally, a single exposure to social defeat stress in rats increases burst firing and DA release in the NAc core[52]. Specifically, this elevated firing occurs as the rat is confronting an aggressor and remains slightly elevated after return to the home cage. An increase in DA firing rate after acute stress correlates with the previously discussed data highlighting increases in DA concentration and metabolism after acute stress.

vRats that are subjected to chronic cold stress undergo a decrease in the number of spontaneously active DA cells compared to control animals[53]. The firing rate and percentage of spikes fired in bursts are not significantly altered as compared to control animals. However, the distribution of bursting across VTA and SN cells differs between the two groups. The decrease in active DA cells with a chronic stressor correlates with data showing decreased levels of DA in target regions after chronic stress[37, 38]. This data also suggests that chronic stress may inactivate one population of DA neurons while increasing burst activity in another. There is evidence that populations of DA neurons possess the ability to switch from single spiking mode to burst firing mode[45]. These populations may represent DA neurons that project to different target regions such as PFC, NAc, BNST or CeA. Different DA populations and their projections may mediate unique responses to stress, perhaps via a diverse sensitivity to stress or ability to mediate a switch in DA neuron firing in response to acute or chronic stress.

Extreme stress may produce diverging results in humans with some people subject to pathological conditions which may lead to depression, anxiety or post-traumatic stress disorder (PTSD), while other individuals appear to escape relatively unharmed. Recent studies in mice attempted to tackle this problem. Cao and colleagues separated mice into susceptible and resilient groups based on their social avoidance behavior after undergoing ten days of social defeat stress[54, 55]. Their studies show that the rate of spontaneous firing and number of bursting events within VTA DA neurons are increased in susceptible but not resilient mice[55]. Chronic social defeat stress increases I_h, a hyperpolarization-activated cation current[55]. I_h has been shown to contribute to the autonomous pacemaker activity of certain neurons and is thought to be activated by the large hyperpolarization following an action potential[56-58]. Therefore, an increase in the size of I_h would facilitate an increase in firing rate or bursting activity. Previous data discussed earlier in the review, details a decrease in spontaneously active DA cells, as well as a decrease in DA concentration and metabolism after chronic stress. One explanation may be that in "susceptible" animals, a greater number of populations of DA neurons make the switch to burst firing after chronic stress. Chronic stress in susceptible animals may be recruiting more components of the DA system than in resilient animals.

Modulation of dopamine firing by norepinephrine

Since stress modifies the firing properties of DA neurons and NE is thought to be a "stress neurotransmitter," it can be postulated that the actions of NE inputs may be partially responsible for the stress effects of DA. The A10 and A10dc DA populations receive substantial NE input, and adrenergic receptor (AR) subtypes are expressed within midbrain dopaminergic areas[26, 59, 60]. Specifically, there is evidence of α_1-AR, α_2-AR and perhaps low levels of β-AR expression in midbrain DA areas[59-61]. There are a few examples of NE producing actions that modulate the firing of DA neurons. A series of studies done by Grenhoff and colleagues show that *in vivo* electrical stimulation of the rat LC and administration of drugs acting on adrenergic receptors can alter DA cell firing within the SNc and VTA[62-65].

Furthermore, it was found that clonidine, an α_2-AR agonist, "regularizes" firing and in some VTA cells, decreases the amount of spikes fired in bursts[63, 64]. This effect was blocked by the α_2-AR antagonists, yohimbine and idazoxan. In fact, the α_2-AR antagonists actually increase burst firing to a level beyond baseline[64, 65]. Application of prazosin, an α_1-AR antagonist, was found to decrease burst firing[65]. In support of this data, Guiard and colleagues also found an α_2-AR mediated decrease in DA firing[66]. Taken together, this data may indicate that NE release onto DA neurons may increase burst firing through postsynaptic α_1-ARs, and this firing can either be increased or decreased through blockade or activation of presynaptic α_2-ARs, respectively.

Paladini and Williams demonstrate that iontophoretic application of NE onto VTA DA neurons in rat brain slices causes an outward current[67]. This outward current can be completely blocked by prazosin and is therefore mediated through the α_1-AR. Furthermore, activation of α_1-ARs causes internal calcium stores to be mobilized. The outward current has a reversal potential near that of potassium and can be blocked by apamin. Collectively, this data indicates that the NE activated outward current is mediated by SK channels which are activated by calcium. Based on these results, NE application and activation of α_1-ARs lead to an inhibition of DA neuron firing while, in the Grenhoff studies, activation of α_1-ARs leads to an increase in burst firing of DA neurons. There are a few possible explanations for this discrepancy. First, in the Grenhoff studies the recordings were done *in vivo* with the drugs applied systemically, but in Paladini and Williams study the recordings were done in *ex vivo* brain slices and drugs were applied iontophoretically directly to the slice. These application variations may cause different NE inputs to be recruited that have unique effects on DA output. Also, the duration of agonist application is very different, with iontophoresis leading to a transient activation of α_1-ARs while the *in vivo* studies will lead to prolonged agonist activation. Indeed, Paladini and Williams found that prolonged application of phenylephrine, an α_1-AR agonist, produces an inward current which would lead to stimulation of DA burst firing as demonstrated in the Grenhoff studies. Iontophoretic application of NE by Guiard and colleagues also leads to a decrease in DA firing[66].

There is also evidence of adrenergic modulation of I_h, the hyperpolarization activated cation current, in putative VTA DA neurons of rat brain slices. Application of clonidine or UK-14304, selective α_2-AR agonists, lead to an inhibition of spontaneous firing and I_h in DA neurons[68]. The inhibition in I_h can be blocked by yohimbine and RS79948, two selective α_2-AR antagonists. RX821002, an antagonist specific for the α_{2A}-AR and α_{2D}-AR subtypes, fails to block the I_h inhibition. Therefore, this modulation of I_h appears to act through the α_{2C}-AR subtype. Further study indicates that I_h inhibition is independent of cAMP levels and instead results from the activation of protein kinase C (PKC). These results are in concordance with the Grenhoff studies, in which activation of α_2-ARs lead to a decrease in firing rate in vivo. Further work needs to be done in this area to determine how NE influences DA firing and the influence of different NE inputs on DA cell firing.

Modulation of excitatory transmission on dopamine neurons by norepinephrine

Stimulation of glutamate afferents facilitates the switch from pacemaker firing to burst firing in midbrain DA neurons[43, 44]. Plasticity at glutamatergic synapses has been found to underlie many learned behaviors[69]. It is possible that changes in glutamatergic transmission occur on DA neurons following acute or chronic stressors. These changes would affect the firing, especially burst firing, of DA neurons. There is evidence that orexin and corticotropin releasing factor (CRF) are powerful modulators of excitatory transmission within the VTA[70]. However, there is very little evidence of NE modulation of glutamatergic transmission on DA neurons in the VTA. Norepinephrine has been shown to modulate excitatory transmission in several other limbic brain regions. For example, it has been shown that activation of α_{2A}-ARs leads to a depression of excitatory transmission and activation of β_1-ARs enhances excitatory transmission within the BNST[71, 72]. In the hippocampus, activation of β-ARs also leads to an enhancement of glutamatergic transmission[73]. Since there are NE inputs in the VTA , as well as evidence of multiple AR subtypes, it is reasonable to hypothesize that NE will modulate glutamatergic transmission onto DA neurons. In fact, unpublished preliminary evidence from our lab indicates that NE leads to an increase in the frequency of spontaneous EPSCs on DA neurons within the RLi. However, there is a great need for studies investigating the role of NE in modulating glutamatergic transmission onto neurons within the VTA subregions and A10dc DA populations.

There is evidence of NE altering mGluR-mediated inhibitory glutamatergic transmission onto VTA DA neurons. Amphetamine may have actions that work to increase DA concentration by altering the firing of midbrain DA neurons, rather than merely altering the function of the dopamine transporter[74]. In this study, amphetamine inhibits mGluR mediated IPSPs with no effect on ionotropic mediated EPSCs. It was determined that this effect can be

blocked by prazosin, an α_1-AR antagonist. Inhibition of the mGluR mediated hyperpolarization may lead to an increase in burst firing of DA neurons and increased DA release. Taken together, this data and previous data indicating an increase in DA burst firing following acute stress lends support to the hypothesis that stress modulates DA firing through the actions of NE.

Conclusions

Acute stress increases DA concentration and metabolism in target regions, while chronic stress may lead to a decrease in DA concentration. Exposure to stressors also leads to an increase in Fos staining and alters the firing of DA neurons. It is possible that these actions of DA in the stress response are mediated by an NE input. The firing of DA neurons can be modulated by NE. Although there seems to be some controversy, it appears that activation of α_1-ARs increases burst firing of DA neurons, but activation of α_2-ARs has an inhibitory effect on DA neuron firing. There is little evidence of NE modulation of glutamatergic transmission onto DA neurons but it is a likely possibility and requires further investigation. Much of the work done regarding stress and DA has been focused on the "classical" VTA and its projections to the mPFC or NAc. However, the BNST and CeA also receive dopaminergic input and play important roles in mediating stress and anxiety behaviors. Dopamine within the BNST has been shown to increase the frequency of spontaneous EPSCs, and in the CeA DA inhibits evoked IPSCs[75, 76]. These actions of DA will alter the output of the extended amygdala and lead to behavioral changes. Therefore it is important to study the effects of stress and NE in the populations of DA neurons that primarily project to the CeA and BNST. Hasue and Shammah-Lagnado found that the extended amygdala receives the majority of its DA innervation from the RLi and CLi regions of the VTA and the A10dc DA neurons arising from the PAG and DR[14]. The A10dc DA neurons have been shown to play roles in the sleep-wake cycle and heroin reward, but there are no studies investigating their role in stress[27, 77]. Moving forward, further investigation into these DA populations that project to the extended amygdala will be required to advance our understanding regarding dopamine's role in the stress response.

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This paper shows increases in burst firing in dopamine

neurons of the rat VTA after exposure to restraint stress. Increases in burst firing lead to an increase in dopamine release in target regions. This is one of the first papers to show the effects of stress on dopamine neuron firing in awake animals.

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Further Information: Lab website http://www.mc.vanderbilt.edu/root/vumc.php?site=winder