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Role of Mesolimbic Brain-Derived Neurotrophic Factor in Depression

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Abstract

Brain-derived neurotrophic factor (BDNF) is widely accepted as being critical for neural and synaptic plasticity throughout the nervous system. Recent work has shown that BDNF in the mesolimbic dopamine (DA) circuit, originating in ventral tegmental area (VTA) DA neurons that project to the nucleus accumbens (NAc), is crucial in the development of depressive-like behaviors following exposure to chronic social defeat stress (CSDS) in mice. While BDNF modulates DA signaling in encoding responses to acute defeat stress, BDNF signaling alone appears responsible for the behavioral effects after CSDS. Very different patterns are seen with another widely used chronic stress paradigm in mice, chronic mild stress (also known as chronic variable or unpredictable stress), where DA signaling but not BDNF signaling is primarily responsible for the behavioral effects observed. This review discusses the molecular, cellular, and circuit basis of this dramatic discrepancy which appears to involve the nature of the stress involved, its severity and duration, as well as its effects on distinct cell types within the VTA-to-NAc mesolimbic circuit.

Keywords

BDNF; Dopamine; Social defeat stress; Chronic mild stress; Depression; Animal models; Electrophysiology; Mesolimbic dopamine circuit; Nucleus accumbens; Ventral tegmental area; Individual differences

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BRIEF INTRODUCTION TO MESOLIMBIC BDNF SIGNALING

BDNF is the most extensively studied neurotrophin and is highly regulated in a neuronal activity-dependent manner (1). BDNF and its receptor, TrkB, are expressed in the mesolimbic dopamine (DA) circuit, which projects from midbrain DA neurons in the ventral tegmental area (VTA) to the nucleus accumbens (NAc) in the basal forebrain (2, 3). This mesolimbic BDNF-TrkB signaling pathway was first implicated in the actions of drugs of abuse over two decades ago (4–6), and has more recently been associated with a range of motivation- and natural reward-related behaviors, including consumption of food and social interaction (7, 8) (Figure 1A). The mesolimbic DA circuit is activated by several forms of physical and social stress (8–10) as well as by natural and drug rewards (8, 11–17). Increasing evidence suggests that interactions between BDNF-TrkB and DA signaling in the mesolimbic circuit play a critical role in stress- and reward-related behaviors (15, 16, 18–20). There is also growing evidence for distinct subsets of VTA DA neurons, based in part on different inputs and outputs, which respond very differently to aversive vs. appetitive stimuli and mediate very different responses to those perturbations (21–23).

Mesolimbic BDNF-TrkB signaling has been implicated as well in the pathophysiology of major depressive disorder (MDD) (24–28), for which antecedent stress is the strongest known risk factor (29, 30). Since loss of pleasure and motivation are core symptoms of depression in humans (31, 32), it is not surprising that dysregulation of the mesolimbic DA system is associated with depression-related behaviors (28, 31, 33). Indeed, manipulation of BDNF-TrkB signaling in the mesolimbic DA system exerts robust effects on stress responses in animal models for depression, with activation of the pathway promoting depression-related behavioral abnormalities (8, 10, 11, 34–36). Clinical evidence confirms these findings. Increased levels of BDNF protein in NAc are reported in MDD patients at autopsy, including individuals who are depressed at the time of death despite being on antidepressants, suggesting elevated BDNF signaling as a sign of treatment-resistant MDD (11). Electroconvulsive therapy, one of the most effective treatments for depression, induces an antidepressant-like effect by reducing VTA BDNF expression (37). This pro-depressant role for BDNF signaling in the mesolimbic circuit is opposite to the well-described antidepressant-like role in other brain regions, in particular, hippocampus and prefrontal cortex (PFC) (see (27, 30, 38, 39). There is a high comorbidity of depression and drug addiction, and indeed studies support the involvement of BDNF in the VTA-to-NAc circuit in contributing to such interactions (40–48).

In this review, we highlight the actions of BDNF-TrkB signaling in the VTA-to-NAc DA system as a key mediator of depressive-like behaviors in the context of chronic stress. Furthermore, we discuss that exposure to different types of stress, through divergent interactions between BDNF and corticotropin-releasing factor (CRF) signaling, may differentially regulate depressive-like behaviors based on cell type-specific actions within the mesolimbic circuitry.

MODELING FOR DEPRESSION IN RODENTS

MDD is a leading cause of severe social and economic burden that affects over 300 million people worldwide (49). MDD is ~35% heritable but this heritability is likely mediated by many hundreds of genes (50), each of which contributes a minute fraction to the overall risk. In the absence of a causative genetic factor of strong effect and high penetrance, the field has relied on several types of chronic stress paradigms in rodents based on epidemiological data which show that early-life trauma and stressful life events are robustly correlated with high risk for depression, signifying aberrations in stress-coping capacity in depressed patients (51–57). A related approach is to expose rodents chronically to corticosterone to mimic one well-characterized concomitant of a chronically-stressed state (58).

Depression is highly heterogeneous, which makes it impossible for any single animal model to capture the entire human condition. Rather, the goal is to induce subsets of depression-like behaviors in animals (59). Some of the most prominent symptoms of depression (e.g., guilt, suicidality, and sad mood) are not accessible in animals. However, other symptoms of depression, schizophrenia, and ASD (e.g., anhedonia, social withdrawal, and alterations in sleep, appetite, and circadian rhythms) are readily measurable in laboratory animals (60, 61). Furthermore, these symptoms induced in rodents after chronic stress can often be ameliorated by administration of medications that are antidepressant in humans, with other classes of medication (e.g., anxiolytic drugs) being ineffective (62, 63)

Traditionally, three criteria are used to judge the validity of an animal model (61). Construct or etiological validity refers to the model recapitulating the causes or mechanisms of a human condition. Face validity means that the model produces symptoms in animals that resemble those of the human illness. Predictive validity indicates that the model reliably and accurately detects treatments that are clinically useful (64, 65). It is important to note that the validation provided for a given model is fit-for-purpose because animal models are used for a variety of objectives where, for example, construct or face validity may have a higher priority for researching potential etiology, whereas predictive validity is essential for medication testing (66). Difficulties in validating animal models for depression have been highlighted (61, 67). Despite the healthy skepticism with which animal models of any psychiatric syndrome should be viewed, recent transcriptomic data have confirmed the ability of chronic stress models in rodents to recapitulate large subsets of gene expression abnormalities seen in human MDD (68), thus establishing that it is possible to induce significant portions of the molecular pathology of human depression in rodent models.

Historically, most studies utilized acute stress assays, such as the forced swim and tail suspension tests (69–71), to study depression-related phenomena, in particular, to screen for potential antidepressant compounds, due to their ease, automation, and rapid phenotyping abilities (60). However, these tests cannot be viewed as models for depression: they utilize acute stresses (which generally does not cause depression) and monoamine-based antidepressants work in these assays after single doses, even though their clinical efficacy requires weeks or months of treatment (60, 72). For these reasons, the field has turned increasingly to a variety of chronic stress models which show better construct and face validity as well as better predictive validity in that they respond only to repeated

administration of monoamine-based antidepressants. Moreover, as stated earlier, studies of human post-mortem samples have shown that chronic stress paradigms induce molecular, cellular, and circuit abnormalities seen in human depression (e.g.,(11, 13, 68, 73, 74). Other models for the study of depression have focused on periods of early life stress (75, 76), which are not covered here because there has been less exploration of the influence of BDNF-TrkB signaling in these paradigms.

ROLE OF VTA DA NEURON ACTIVITY IN CHRONIC STRESS MODELS: CMS VS. CSDS

Chronic mild stress (CMS)—also referred to by some as chronic variable or unpredictable stress—is one of the most widely used chronic stress-based animal models for depression (77). In the CMS model, animals are subjected to varied and intermittent physical stressors such as forced swim test, cage tilt, cage crowding, and water and food deprivation over a period of time that ranges from 1 – 12 weeks (60, 78, 79). Animals exposed to CMS display increased immobility in the forced swim and tail suspension tests, and a decrease in social interaction and sucrose preference, used as rough measures of anhedonia (38, 80–82). More precise determinations of anhedonia would involve more time-consuming operant behaviors, which have rarely been used in the field but represent an important goal for future studies. Mice exposed to CMS exhibit decreased activity of VTA DA neurons (80, 82), an effect observed in brain slices *ex vivo* and in awake mice *in vivo*. Acute, optogenetic phasic (30 Hz) stimulation of VTA DA neurons reverses the CMS-induced abnormalities in sucrose preference and tail suspension tests (38, 80, 82) (Figure 1B, C). In contrast, optogenetic inhibition of VTA DA neurons in stress-naïve mice reduces sucrose preference and increases immobility (80).

A recent study with brain slices *ex vivo* has shown that the reduced firing activity of VTA DA neurons seen after CMS is specific for VTA-to-PFC DA neurons, with no effect observed for VTA-to-NAc DA neurons (38). A similar lack of effect of CMS was found for the lateral VTA (83), where DA neurons project predominantly to NAc (84). In contrast, other studies found significant reductions in firing rate and burst firing in lateral VTA DA neurons after CMS (80, 82). This discrepancy may be due to differences in the CMS paradigms used: the former studies applied 3–4 stressors/week over 4 weeks in rats (83) and 5–7 stressors/week over 5 weeks in mice (38), whereas the latter studies applied 14 stressors/week over 5 weeks in mice (82) and 14 stressors/week over 8–12 weeks in mice (80).

The reported differences in neural activity between VTA-to-NAc and VTA-to-mPFC circuits following CMS may be partly due to differences in expression of ion channels between circuits. Recent studies demonstrated that there are large hyperpolarization-activated cyclic nucleotide-gated (HCN) channel-mediated currents (I_h) in VTA-to-NAc DA neurons, but small or no I_h in VTA-to-mPFC DA neurons (84, 85). Pharmacological manipulations that increase I_h in VTA DA neurons increase firing frequency (85–88). CMS reduces I_h in VTA-to-NAc DA neurons (82), with a consequential reduction of DA release in NAc (89). Likewise, shRNA-mediated knockdown of HCN2 in VTA mimics CMS-induced depressive-

like behavior in stress-naïve mice, whereas overexpression of HCN2 in VTA prevents the CMS-induced behavioral deficits (82). These findings emphasize that reduction in DA signaling in the VTA-to-NAc DA pathway contributes to depressive-like behaviors induced by CMS (Figure 1C), although as noted in the previous paragraph there are studies that suggest a predominant effect of CMS on VTA-to-PFC DA neurons.

The ion channel mechanisms that underlie stress-induced regulation of VTA-to-PFC DA neurons remain unknown. In contrast, very different effects are seen after chronic social defeat stress (CSDS), another well-established mouse model for depression (8, 11). Ten days of CSDS causes social avoidance in a subset of mice, which are designated as 'susceptible' to CSDS; the remainder are designated 'resilient'. The susceptible mice also exhibit reduced sucrose preference, as well as disrupted circadian, sleep, and feeding behavior, compared with resilient and stress-naïve control mice (8, 11, 60, 90, 91). Strikingly, susceptible mice exhibit increased firing activity and burst firing in VTA DA neurons in brain slices *ex vivo* and in anesthetized mice *in vivo*, respectively (9–11, 88, 92–94) (Figure 1D). Moreover, this effect is specific for VTA-to-NAc DA neurons, with the opposite effect—a reduction in firing activity—observed for VTA-to-PFC DA neurons (10). Optogenetic inhibition of VTA DA neurons in general, or VTA-to-NAc DA neurons specifically, in susceptible mice induced a rapid antidepressant-like response: the manipulation increased social interaction and sucrose preference behaviors (10). Conversely, in a one-day subthreshold social defeat stress (sub-SDS) procedure that does not induce behavioral abnormalities, phasic activation of either VTA DA neurons in general, or VTA-to-NAc DA neurons specifically, during the social interaction test induced depressive-like behavior, effects not seen in stress-naïve control mice (10, 34). These lines of evidence that VTA-to-NAc and VTA-to-PFC pathways have distinct functional properties and differentially regulate behavior suggest that aversive stimuli differentially affect these microcircuits and that the final behavioral output results from the balance between these circuits.

In contrast to CMS, CSDS increases I_h in VTA DA neurons of both susceptible and resilient mice, compared to non-stressed control mice (9, 85). The enhanced I_h increases VTA DA neuron activity and DA release in NAc (85–87, 95) (Figure 1D). It is of particular interest that resilient mice display a greater magnitude of induction of I_h in VTA DA neurons compared to susceptible mice, and that this greater I_h induction triggers stable normal firing of VTA DA neurons in resilient mice. This occurs via the homeostatic induction of several types of potassium (K^+) channels in the resilient VTA which normalizes VTA DA neuron firing and promotes resilience to defeat stress (11, 85) (Figure 1E). Overexpression of the inwardly rectifying K^+ channel Kir2.1 in VTA of susceptible mice decreases the firing rate of VTA DA neurons and blocked social avoidance behaviors (11), similar to intra-VTA infusion of an I_h channel inhibitor (9). Studies in primary neuronal cultures have reported that excessive hyperactivity can induce homeostatic up-regulation of K^+ channel-mediated current (96). Our observation that elevated K^+ current attenuates the I_h current-induced increase in DA neural activity in resilient mice suggests that homeostatic plastic processes occurring in the mesolimbic region stabilize neural dynamics (85).

Recent evidence further highlights the role of ionic channels in VTA DA cells in mediating resilience to social stressors. Overexpression of KCNQ3 (Kv7.3), a slow voltage-activated K

$^{+}$ channel which is induced in VTA of resilient mice (11), specifically in VTA DA neurons of susceptible mice reversed both the increased firing of VTA DA neurons as well as the depressive-like phenotype (97). Thus, targeting KCNQ channels offers a novel approach for depression treatment, since intra-VTA infusion or systemic administration of KCNQ channel openers, including the FDA-approved drug retigabine (also called ezogabine, originally approved as an antiepileptic drug) (98), normalized depression-like behaviors in susceptible mice (97). A recent open-label clinical trial with 18 medication-free MDD patients found that retigabine had significant antidepressant efficacy, along with normalizing depression-related functional connectivity abnormalities in the brain's reward circuitry (99), a finding now being followed up with a placebo-controlled study. While these clinical data should be viewed with caution since retigabine has several side effects (98), the observations demonstrate the ability to apply insight derived from rodent stress models to novel approaches for the treatment for depression (99, 100).

The differences observed in VTA DA neuron activity, and in I_h in these cells, after CMS vs. CSDS might be explained by the type and intensity of the stressor as well as by the duration of stress exposure (79, 101, 102). Strong stress increases VTA DA neural activity (103), whereas milder stress decreases it (94, 104). These findings likely correlate with observations that CMS, which typically consists of exposing mice to a variety of weak but uncontrollable stressors, decreases VTA DA neural activity, while CSDS which consists of more severe and socially-relevant stress increases such activity. However, we observed that evoked DA release in NAc is not significantly altered by CSDS, which may reflect a ceiling effect of CSDS increased phasic firing of VTA DA neurons *in vivo* (35). This discrepancy between DA release and DA neural activity following CSDS may be also related to CRF, a neuropeptide released in response to stress (105), that may play a prominent role in regulating DA neural activity or DA release. CRF positively mediates rewarding behavior by enhancing I_h in VTA DA neurons, which leads to elevated evoked DA release in NAc of stress-naïve animals (95). In contrast, severe-stress exposure completely ablated the CRF effects on DA release and subsequent appetitive behaviors (106). This switch in CRF action on DA release is mediated in part by glucocorticoid signaling associated with severe and chronic stress (106).

ROLE OF BDNF AND CRF IN CSDS: ACUTE VS. CHRONIC ACTIONS

Both CMS and CSDS, as described above, show causal evidence that acute manipulations of VTA DA neurons can alter depressive-like behaviors in a range of behavioral assays (107). However, there are some intriguing reports that DA-deficient mice (generated through loss of DA-synthetic enzymes) can still learn and express preferences for sucrose (108), and that pharmacological depletion or antagonism of mesolimbic DA signaling does not alter sucrose preference in stress-naive animals (109). These data suggest that DA *per se* is not always the critical mesolimbic substrate in some types of stress-based depression models.

As noted earlier, CSDS increases BDNF protein levels and BDNF-TrkB signaling in NAc, effects dependent upon the *Bdnf* gene in VTA DA neurons (8, 11). Knockout of *Bdnf* in VTA blocks behavioral susceptibility to CSDS and exerts antidepressant-like effects (Figure 1D) (8, 11, 37). Blockade of BDNF-TrkB signaling in NAc also has an antidepressant-like

effect (11, 35, 36), while increasing BDNF levels in NAc produces pro-depressant effects (11). These actions of mesolimbic BDNF in the CSDS model are in striking contrast to the lack of influence of BDNF in the CMS model (38, 110). For example, CMS does not alter protein levels of BDNF in either NAc or VTA (110). BDNF infusion into NAc shell has no impact on CMS-induced depressive-like behaviors (38).

Insight into the relatively contributions of DA and BDNF to stress responses comes from a study, which demonstrated that BDNF-TrkB, but not DA, signaling in NAc is essential for CSDS-induced depressive-like abnormalities (35). Chronic optogenetic phasic stimulation of VTA-to-NAc circuit during CSDS exacerbated defeat-induced behavioral symptoms, and these aggravated symptoms were reversed by blockade of BDNF-TrkB signaling in NAc. By contrast, optogenetic activation of VTA-to-NAc DA neurons during CSDS, or CSDS itself, did not alter evoked NAc DA release (35). Additionally, intra-NAc infusion of DA receptor antagonists had no effect on CSDS-induced depressive-like symptoms (35). This inability of DA signaling to affect CSDS-induced depressive-like behaviors is very different from sub-SDS, where intra-NAc administration of DA receptor antagonists blocked the ability of acute optogenetic stimulation of VTA-to-NAc circuit to induce depressive-like behaviors following sub-SDS (Figure 1D, G) (35). This difference in the role of mesolimbic DA signaling between Sub-SDS and CSDS may be due to mesolimbic BDNF normalizing stress-induced extracellular DA release in NAc where CSDS-induced BDNF signaling in VTA-to-NAc pathway may attenuate DA release that can be facilitated by heightened mesolimbic DA activity, a mechanism supported by studies in BDNF+/– mice (111–113).

In contrast, the significant effect of DA signaling on depressive-like behaviors in sub-SDS could be associated with lack of involvement of CRF, whose regulation of the mesolimbic system becomes prominent only after severe, chronic stress (35, 106). One day of sub-SDS may not be long enough for CRF action to switch from appetitive to aversive, compared to CSDS. In other words, in contrast to CSDS, one-day sub-SDS increases DA activity in the context of normal CRF action, mediating appetitive behaviors (92, 106, 114), which may explain the previous observation that sub-SDS sometimes increases social interaction (11, 115) (Figure 1F). Observations that phasic stimulation of VTA-to-NAc DA neurons, following sub-SDS, requires NAc BDNF signaling in order to induce depression-like behavior, while intra-NAc infusion of a CRF receptor antagonist reverses both social avoidance and BDNF release, suggests an intimate interaction between these systems in encoding for the actions of acute stressors (34) (Figure 1G).

DOWNSTREAM TARGETS OF BDNF ACTIVATION – D1 VS. D2 MSNs

Principal NAc neurons are categorized as D1-type or D2-type medium spiny neurons (MSNs) based on the predominant DA receptor that they express. In general, D1 MSNs send projections to VTA and to a lesser extent to ventral pallidum, while D2 MSNs send projections to ventral pallidum (116, 117). These two neural populations work in concert to control behavior, with an imbalance promoting dysfunctional motivational states (118–122). In general, activation of D1 MSNs promotes rewarding behavior, while activation of D2 MSNs exerts the opposite effect (119, 122–126).

Stress exposure has also been shown to differentially affect these neuronal subtypes. D1 MSNs were shown to be the site of action of BDNF in NAc following CSDS exposure. Levels of phosphorylated (active) ERK, a downstream target of TrkB receptor signaling, are increased solely in NAc D1 MSNs of susceptible, but not resilient, mice (35, 97). These observations suggest that BDNF signaling in D1 MSNs contributes to the susceptible phenotype after CSDS (Figure 1D). Interestingly, enhanced ERK phosphorylation has been associated with reduced neuronal activity of D1 MSNs (122), and reducing neuronal activity of D1 MSNs renders resilient mice more susceptible (126). Moreover, excitatory synaptic input to D1 MSNs is reduced in susceptible mice after CSDS (126) and in mice subjected to repeated restraint stress (127), both of which induce anhedonia-like behaviors. Together, these results support a scheme wherein increased BDNF signaling in NAc contributes to CSDS-induced behavioral susceptibility by inhibiting the activity of D1 MSNs. *In vivo* imaging studies report decreased activity of D1 MSNs of susceptible mice (128). In contrast, enhanced activity of D1 MSNs encodes pro-reward and reinforcement behaviors (122, 126, 127, 129–131). D2 MSNs exhibit increased excitatory synaptic input in susceptible mice after CSDS, which suggests possible differences in the effects of phasic VTA DA input to D1 vs. D2 MSNs in NAc. In other words, it is possible that elevated BDNF release from VTA DA nerve terminals in NAc in response to CSDS has differential effects on D1 and D2 MSNs resulting in the expression of depression-like behaviors.

The transcription factor EGR3 is another promising downstream target of mesolimbic BDNF activation (132). Following exposure to CSDS, EGR3 is upregulated in NAc D1 but not D2 MSN's of stress susceptible mice (128). Furthermore, elevated EGR3 appears to be responsible for the observed decreased excitatory input and increased dendritic atrophy in D1 MSNs of stress susceptible mice (128). EGR3 regulates the expression of several proteins involved in synaptic plasticity and ChIP-seq analysis found that stress exposure altered EGR3 binding to promoter regions of genes involved in dendritic morphology, such as *Actn1*, *RhoA*, and *Shank2* (128, 133, 134). In light of earlier work that stress susceptible mice exhibit elevated phasic activity of VTA DA neurons (10, 11) and concomitant enhanced levels of BDNF release from VTA DA terminals in NAc (11, 34), it is possible that the elevated BDNF induces EGR3 in D1 MSNs leading to decreased excitatory input and increased dendritic atrophy (128) and subsequent expression of depression-like behavior (Figure 1D).

Exposure to CSDS differentially induces expression of another transcription factor ΔFosB, which accumulates in NAc in response to repeated stimuli associated with reward, motivation, or stress (135). Mice susceptible to CSDS exhibit ΔFosB induction selectively in D2 MSNs, while those resilient to CSDS show ΔFosB induction solely in D1 MSNs (136). Chronic exposure to drugs of abuse also induces ΔFosB expression in NAc, with effects predominating in D1 MSNs, although opiate drugs of abuse and natural rewards induce the protein in both cell types (136, 137).

A recent study investigated whether the observed comorbidity between addiction and depression may be related to overlapping signaling between BDNF and ΔFosB within the mesolimbic circuit. This study followed up on previous observations that intra-VTA BDNF overexpression enhanced social defeat stress-induced cross sensitization to psychostimulants

together with induced ΔFosB expression in NAc (138). The authors showed that, while stress exposure increased cocaine intake, rats exposed to social defeat stress together with increased expression of VTA-BDNF exhibited even greater cocaine intake and increased ΔFosB expression in NAc. BDNF-TrkB signaling in NAc activates the transcription factor CREB (139, 140), as would be expected since CREB activation is known to be downstream of TrkB activation. The observation that CREB induces ΔFosB transcription (141, 142) and itself can promote depression-like behavior at the level of VTA-to-NAc circuit (28), suggests complex feedback loops that operate within NAc MSNs—in a cell-type specific manner—to control the influence of BDNF in this circuit and the generation of both depression- and addiction-like behavioral abnormalities. It should be noted that, in addition to distinct D1 and D2 MSNs, there is also a small subpopulation of cells that express both D1 and D2 receptors in NAc, along with reports that functional D1-D2 receptor dimers contribute to regulation of these cells.

Stress hormones also play a role in regulating circuits connecting stress signaling to the mesolimbic system. Certain depression-like behaviors (e.g., social avoidance) after chronic stress require activation of glucocorticoid receptors (GR) on NAc MSNs (143). Knockout of GR from MSNs, but not VTA DA cells, alleviated CSDS-induced depression-like, but not anxiety-like, behaviors. Building upon previous studies (9–11, 34, 85), this group observed increased VTA DA neural activity *in vivo* following exposure to CSDS, which was lost upon GR receptor knockout from MSNs (143). That GR knockout in MSNs alleviates the CSDS-induced increase in VTA DA activity suggests a feedback mechanism from NAc to VTA. Further work is needed to determine whether this normalization of VTA DA neuron activity is mediated by their direct innervation by MSNs or by indirect effects of MSNs on VTA inhibitory interneurons.

CONCLUSIONS AND FUTURE DIRECTIONS

Today’s antidepressant treatments fully treat <50% of affected individuals (144–146). The highly heterogeneous nature of depression has prompted preclinical and clinical researchers to use multiple stress paradigms and clinical measures to define diverse mechanisms that contribute to the etiology of depression toward the goal of more personalized treatments in the future (24). From the preclinical side, for example, work described here has distinguished between acute vs. chronic stress paradigms (35) and between stress-susceptible vs. stress-resilient animals subjected to stress (11, 147). Types, intensity, duration and incubation period of stress have been considered as contributing factors (79, 101, 148).

We speculate that the strength of stressors is a key determinant of the effects on VTA DA neuron activity. Severe stress increases VTA DA neural activity (103), whereas mild stress decreases it (94, 104). These findings are consistent with observations that CMS decreases VTA DA neural activity, while CSDS increases it. Of note is our 2016 study showing that DA release is no longer relevant to the CSDS-induced increase in phasic firing of VTA DA neurons, since evoked DA release in NAc is not significantly altered by CSDS due to compensating mechanisms (Figure 2). In addition, mesolimbic DA signaling was found not to mediate CSDS-induced behavioral abnormalities (35). The lack of DA release and of

functional DA signaling in NAc following CSDS may be related to CRF, whose homeostatic regulation over the mesolimbic system is revealed only after severe, chronic stress (106). It may also be due to homeostatic effects of BDNF on the excitability of DA neurons or on extracellular DA release as observed in previous studies (15, 111–113). Understanding these homeostatic functions of CRF and BDNF and their concomitant interaction in CSDS warrants further investigation.

Current evidence thus supports a scheme where mesolimbic BDNF, which is induced only in susceptible mice after CSDS, contributes importantly to the behavioral sequelae of CSDS, independently of DA signaling. However, this hypothesis raises further questions. What are the molecular and physiological mechanisms that elevate mesolimbic BDNF in response to CSDS? As discussed above, NAc CRF is one candidate to induce mesolimbic BDNF and downstream depressive-like behaviors (34). Alternatively, does NAc CRF act directly on NAc MSNs to induce behavioral susceptibility to CSDS? If so, are D1 MSNs, where BDNF-TrkB signaling mediates the behavioral effects of CSDS, also important for CRF action? It would be interesting to investigate whether CRF-induced release of BDNF from VTA DA nerve terminals into NAc of stress susceptible mice decreases expression of ΔFosB in D1 MSNs or induces ΔFosB in D2 MSNs to also contribute to the susceptible vs. resilient phenotype (135, 136). Taken together, investigating the dynamics of mesolimbic BDNF signaling, and its interactions with numerous other molecular and cellular mechanisms in this circuit, have provided important insight into the biological mechanisms of susceptibility and resilience in response to diverse types of stress, work that is also being mined for developing more effective and better-targeted therapeutics for depressive disorders.

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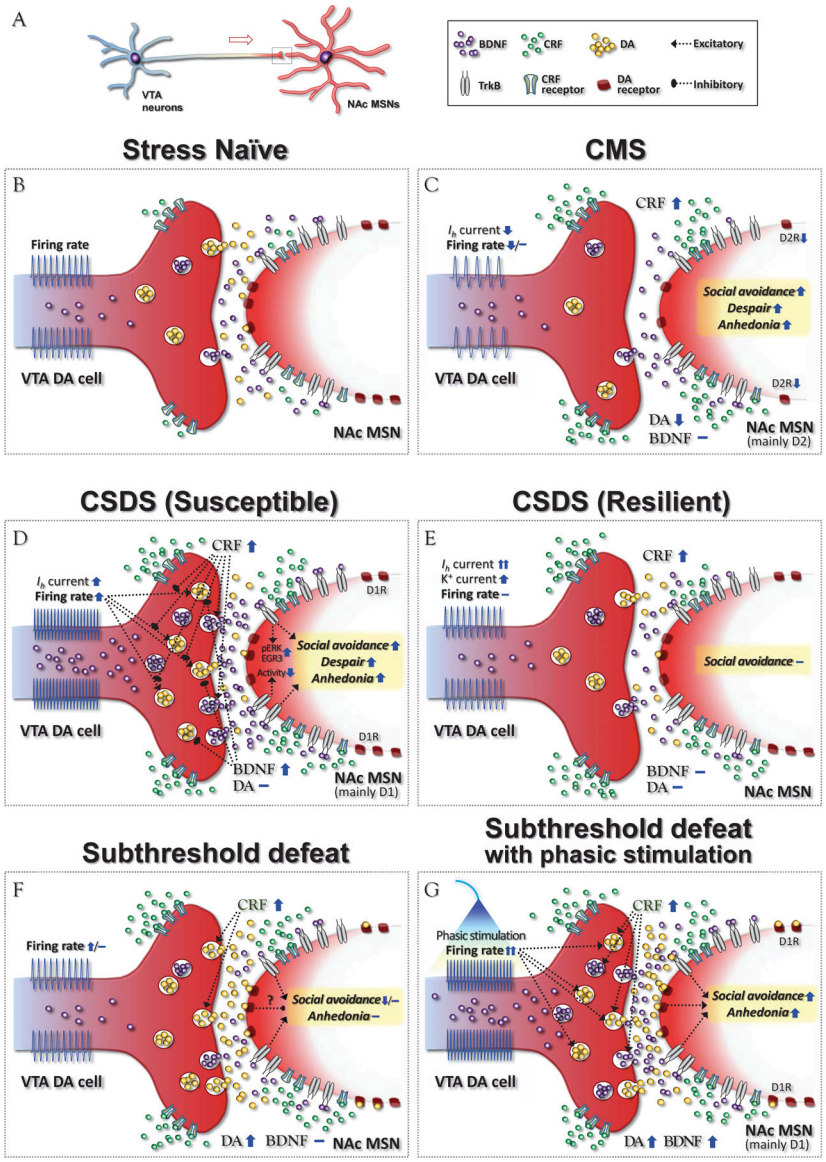

Figure 1.

Role of brain-derived neurotrophic factor (BDNF), and its interactions with dopamine (DA) and corticotropin-releasing factor (CRF), in controlling the mesolimbic circuit after chronic stress. (**A**) The mesolimbic DA circuit, which is composed of DA neurons in the ventral tegmental area (VTA) and their forebrain projection regions, in particular, medium spiny neurons (MSNs) in nucleus accumbens (NAc), has been associated with depressive-like behavioral phenotypes including social avoidance and anhedonia in animal models for depression. (**B,C**) Chronic mild stress (CMS) decreases I_h and firing rate of VTA-to-NAc DA neurons. Some clinical and preclinical studies show antidepressant-like effect of pramipexole, a D2 receptor agonist and relevance of mesolimbic D2 signaling in CMS models, suggesting a functional role of D2 MSNs in depressive symptoms (149–152). However, there are reports of selective effects of CMS on VTA-to-PFC DA neurons (see text). (**D**) In contrast to CMS, animals susceptible to chronic social defeat stress (CSDS)

display increased I_h and firing rate of VTA-to-NAc DA neurons and enhanced levels of NAc BDNF. Nonetheless, evoked DA release in NAc is not altered in susceptible animals, which may be due to homeostatic effects of CRF and BDNF in the mesolimbic circuitry. CRF, which elevates evoked DA release in NAc of stress-naive animals, attenuates DA signaling in NAc in response to excessive and uncontrollable stress. This switch in CRF action may be mediated by changes in glucocorticoid signaling associated with chronic stress (not shown). Studies show that BDNF, but not DA, signaling in the mesolimbic system mediates CSDS-induced depressive behaviors. CSDS-induced BDNF signaling in NAc could contributes to behavioral susceptibility through ERK phosphorylation, EGR3 induction, and its consequential reduction in D1 MSN activity. (**E**) Compared to susceptible animals, highly upregulated I_h, but with normal neuronal activity due to a homeostatic induction of K^+ currents, are observed in VTA-to-NAc DA neurons of resilient mice. (**F,G**) In subthreshold defeat stress paradigm, phasic activation of VTA DA neurons in general, or VTA-to-NAc DA neurons selectively, induces depressive-like behaviors, which is mediated through both BDNF and D1 receptor signaling. In contrast to CSDS, acute and weak stress manipulations such as subthreshold defeat stress elevate DA release via CRF in NAc (see text for details). In addition, CRF is required for NAc BDNF induction and consequent depressive behaviors by phasic activation of VTA-to-NAc neurons in subthreshold defeat stress.

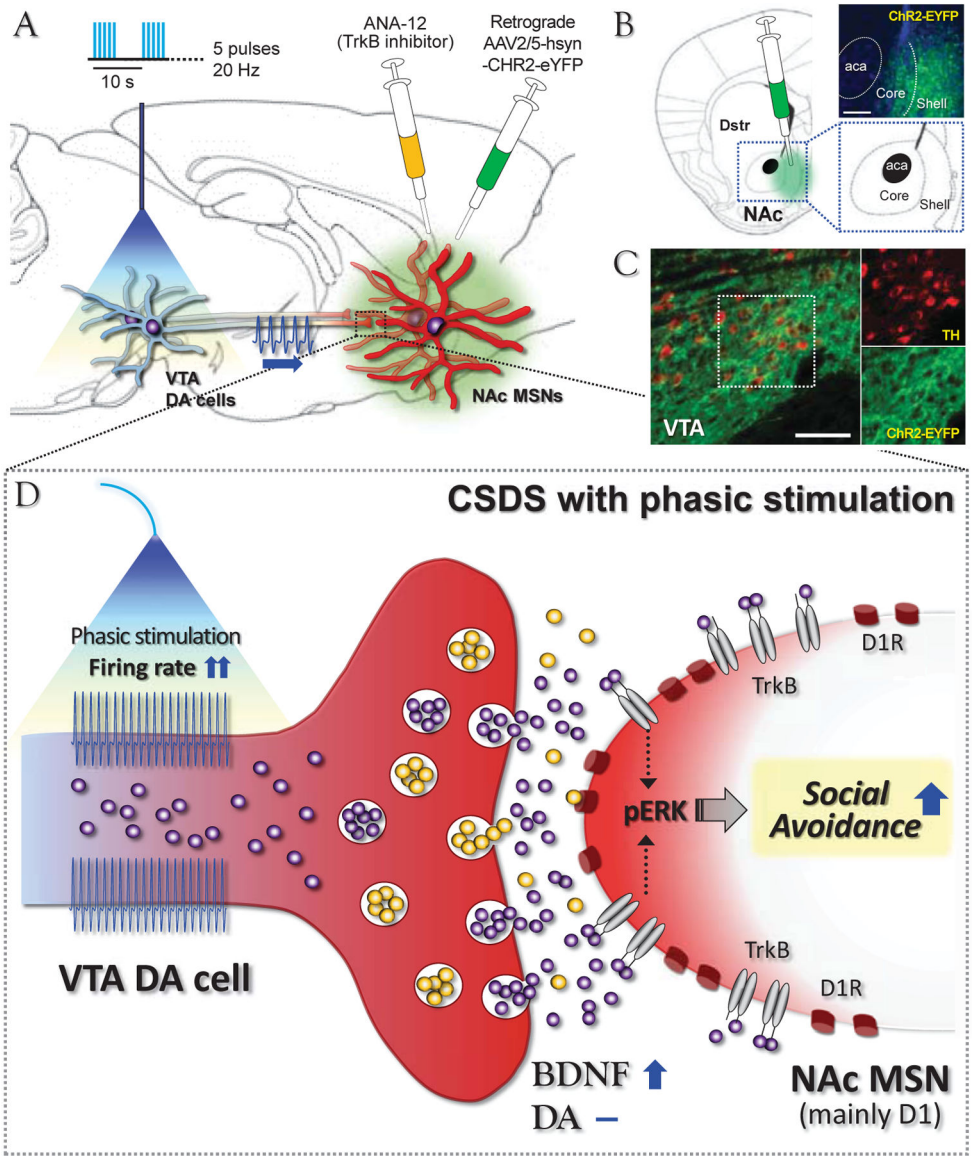

Figure 2.

Working model of behavioral abnormalities (e.g., social avoidance) which are exacerbated by repeated phasic optogenetic stimulation of VTA-to-NAc DA pathway during CSDS. (**A**) Illustration of retrograde AAV2.5-hsyn-ChR2-eYFP infused into NAc, intra-NAc ANA-12 infusions, and optic fiber implantation into VTA. Blockade of D1 or D2 signaling in NAc does not affect social avoidance induced by CSDS, but inhibition of BDNF-TrkB signaling in NAc using ANA-12 reverses this behavioral abnormality (35). Impaired social interaction after CSDS was exacerbated by repeated phasic activation of VTA-to-NAc pathway. Inhibition of BDNF-TrkB signaling blocked this effect of optogenetic stimulation. (**B**) Schematic coronal sections showing injection site of AAV2.5-hsyn-ChR2-eYFP in NAc. Scale bar, 100 μm. (**C**) Representative confocal images showing localization of ChR2-EYFP (green) in TH+ cells (red) in VTA. Scale bar, 50 μm. (**D**) Illustration of CSDS-induced social avoidance behavior which is exacerbated by repeated phasic optogenetic stimulation

of VTA-to-NAc DA pathway. NAc BDNF mediates social avoidance through activation of TrkB on D1 MSNs, as evidenced by exclusive induction of ERK phosphorylation in D1 MSNs of susceptible mice (35).