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Neuroadaptations and TGF-β Signaling: Emerging role in models of neuropsychiatric disorders

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Abstract

Neuropsychiatric diseases are manifested by maladaptive behavioral plasticity. Despite the greater understanding of the neuroplasticity underlying behavioral adaptations, pinpointing precise cellular mediators has remained elusive. This has stymied the development of pharmacological interventions to combat these disorders both at the level of progression and relapse. With increased knowledge on the putative role of the transforming growth factor (TGF- β) family of proteins in mediating diverse neuroadaptations, the influence of TGF-β signaling in regulating maladaptive cellular and behavioral plasticity underlying neuropsychiatric disorders is being increasingly elucidated. The current review is focused on what is currently known about the TGF-β signaling in the central nervous system in mediating cellular and behavioral plasticity related to neuropsychiatric manifestations.

Keywords

TGF-β; Neuropsychiatric disorders; Epigenetics; Synaptic plasticity; Morphological plasticity

1. Introduction

A range of public health problems is associated with the expression of persistent maladaptive behaviors. These persistent and aberrant behaviors form the pathological basis underlying several neuropsychiatric disorders such as Substance Use Disorder (SUD), Anxiety and stress-related disorders. On the surface, these maladaptive behaviors span

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a diverse range of outward manifestations with underlying dysregulated neurobiological adaptations that are often distinct [1]. There is a social stigma attached to such behavioral aberrations as 'voluntary disorders of choice' and often lacks understanding of the neurobiological mechanisms driving such behavioral anomaly [2, 3]. There has been considerable effort in the search for treatments of these diseases necessitating an in-depth understanding of the brain mechanisms underlying these behavioral adaptations. However, the heterogeneous nature of these diseases that are tied to a complex interaction of genetic and environmental factors often makes it cumbersome to pinpoint a single cellular regulator. Here we discuss the role of a conserved family of proteins, transforming growth factor beta (TGF-β), in serving as an essential substrate underlying divergent forms of maladaptive behavioral plasticity. Learning and memory is integral to behavioral adaptations and there is conclusive evidence that TGF-β signaling is essential for neural plasticity underlying these plasticity events [4–7].

The TGF-β superfamily of proteins comprises regulatory polypeptides that perform a wide array of cellular functions encompassing, but not limited to, developmental programming, immune homeostasis, differentiation, translational changes, epigenetic regulation, and morphological plasticity [8, 9]. Due to such ubiquitous role of the TGF-β family of proteins, they are continually being implicated in various diseases. There is a plethora of evidence describing the association of TGF-β pathways and nervous system disorders. Altered TGF-β1 and Activin expression have been reported in diseases such as autism, schizophrenia, Parkinson's disease and Huntington's disease [10–13]. TGF-β pathways are being increasingly implicated in affective disorders making this extended family of proteins an essential target for next generation therapeutics. Further, recent studies have made significant strides in elucidating temporal and mechanistic roles for dysregulated TGF-β signaling following exposure to drugs of abuse such as cocaine, which may influence relapse vulnerability. Here we review and summarize findings in the last decade on how maladaptive behavioral plasticity usurp the TGF-β pathways to disrupt cellular contexts and mediate neuroadaptations that underlie pathological correlates of human psychiatric diseases in preclinical models (Table 1).

2. Receptors and mediators of the TGF-β pathways

TGF-β signal transduction diverges temporally and in the cellular context, which imparts a wide range of functional latitude to this family of proteins relevant to various pathophysiological conditions. The most common contextual and temporal determinants of TGF-β function are categorized into three main types: first, the abundance of TGF ligands and receptors; second, transcriptional regulators and histone modifiers; and finally, the epigenetic status of the cell [14]. Broadly, the TGF-β superfamily consists of a group of bone morphogenetic proteins (BMP), activins (ACT), inhibins (INH), growth and differentiation factors (GDF), and TGF-β proteins [9]. Members of the TGF-β family of proteins signal through dual-specificity kinase receptors that are localized on target cells and exhibit structural similarities with both serine/threonine and tyrosine kinases. Structurally, the receptors consist of: 1) extracellular domain, 2) transmembrane domain, 3) juxtamembrane domain, and 4) kinase domain [9]. Upon activation, the receptor kinases phosphorylate downstream targets that are comprised of receptor-triggered SMAD (*Caenorhabditis elegans*

SMA (“small” worm phenotype) and MAD family (“Mothers Against Decapentaplegic”)) family members. TGF-β, activin, and nodal mechanisms involve SMAD2 and 3, whereas BMPs and GDFs target SMAD1, 5, and 8. The activated phosphorylated SMADs (R-SMADs- receptor regulated SMADs) then associate with SMAD4, a common mediator that allows the complex to be translocated into the nucleus for cooperation with various transcription factors to regulate a wide array of gene expression profiles. SMAD-mediated signaling is referred to as the canonical pathway. TGF-β proteins also function through a SMAD-independent, non-canonical mechanism that triggers extracellular signal-related kinases involving actin dynamics and altered plasticity involving glutamatergic signaling [15].

3. TGF-β mediated neuroplasticity in affective behaviors

Anxiety, depression and stress-related diseases are predominant psychiatric disorders that have disabling effects on individuals and society [16–18]. Currently available treatments for anxiety and depression, which are not effective for some individuals, include response time that range from 3–5 weeks with more than 50% requiring multi-treatment intervention to achieve remission[19]. An overt requirement for improved treatment modalities is therefore essential. However, there have been modest outcomes in terms of identifying predictive genes underlying the pathological basis of these disorders, which hinder alternative therapeutic strategies. Genetic correlation studies have revealed polymorphisms in the TGF-β family of proteins as determinants of antidepressant response [20]. Further, studies in preclinical models described below corroborate the role of these family of proteins in mediating several aspects of neuroplasticity events underlying these maladaptive behaviors.

3.1 Hippocampal canonical TGF-β signaling

3.1.1 Depression—The hippocampus is a limbic structure associated with learning and memory [21, 22]. Hippocampal sub-regions, more specifically, the dentate gyrus (DG) plays an essential role in mediating a balanced regulation of mood and antidepressant efficacy [23]. There is clinical evidence of fewer DG granule cells in the brains of patients suffering from major depressive disorder [24, 25]. This is complemented by studies on preclinical models where DG is established as a critical neural hub mediating the antidepressant response [26–28]. Antidepressants alter the TGF-β family of proteins in the hippocampus of rodent models of depression. Activin, a member of the TGF-β superfamily that functions through type I and II receptor kinases and governs gene expression via SMAD2/3 translocation into the nucleus, is associated with several neuropsychiatric disorders [29]. Chronic treatment with paroxetine upregulates activin A and its receptor Acvr1a in the DG, while SMAD2 phosphorylation is potentiated with fluoxetine [20, 30]. Interestingly, SMAD2 and SMAD3 levels vary among drug responders in clinical cohorts. SMAD2 is increased in clinical responders while SMAD3 is increased in non-responders [31]. Acute infusion of activin A in the DG potentiates the effect of anti-depressant in novelty suppressed feeding task effect in depression tasks, while inhibin A (endogenous inhibitor of activin signaling) infusion occludes the antidepressant-like effect in rodents [31]. Electroconvulsive stimulation (ECS), an alternative treatment in patients with poor response to first-line antidepressant regimen, evokes elevated levels of activin A and downstream target SMAD2 in the hippocampus of rats [30]. Similarly, environmental enrichment, an established method to combat depression-like behavior in

rodents, produces a pronounced elevation of activin A in the hippocampus [32]. These studies point towards a role for canonical activin signaling pathway in the hippocampus involving SMAD2, possibly through SMAD2-dependent epigenetic plasticity, in depression (Fig 1). Indeed, in a mouse model of ECS, SMAD2 chromatin immunoprecipitation of hippocampal lysates reveal upregulation of chromatin remodeler JMJD3 and negative feedback regulator of TGF-β signaling, PMEPA1 [32]. Despite serving as a negative feedback inhibitor of the TGF-β pathway, PMEPA1 is thought to have an extended role in maintaining glial cellular signatures in the brain. There is emerging evidence that PMEPA1 is an important component of microglial homeostatic signature genes required for the central nervous system (CNS) microenvironment that is tightly regulated by neurons and astrocytes involving TGF- β signaling [33]. Though JMJD3 is a histone demethylase, there was no overall reduction in histone 3 lysine 27 tri-methylation (considered as a permissible mark) reported in the hippocampus of the ECS rats. This could be largely due to the loss of tri-methylation on specific genes instead of global changes to tri-methylation patterns rendering these genes available for gene transcription. Conversely, a tri-methylation independent role of JMJD3 cannot be ruled out. Studies have indicated that JMJD3 is essential for microglial plasticity [34, 35] and inflammatory responses [36]. Both microglial and inflammatory dysregulation are integral to psychiatric conditions [37, 38] possibly linking activin signaling to glial plasticity.

Unlike activin signaling that is potentiated due to antidepressant treatment, the BMP signaling is negatively regulated by antidepressants. BMP signaling is downregulated in mice treated with fluoxetine and overexpression of BMP4 in the hippocampus prevents the protective effects of fluoxetine on hippocampal neurogenesis and behavioral amelioration (Fig 1). Further, targeted inhibition and ablation of BMP signaling in the hippocampus and Ascl1 (Achaete-scute homolog 1) expressing progenitor cells produce similar effects of enhanced neurogenesis and attenuation of anxiety- and depression-like behaviors [39].

3.1.2 Stress and Anxiety—Anxiety and stress-related disorders are commonly occurring mental illnesses that have been attributed to an imbalance in hippocampal neurogenesis [40–42]. Transgenic mice that exhibit overexpression of endogenous activin signaling inhibitor, Follistatin, in the forebrain display anxiety-related behavior, and is concomitant with neuronal loss in sub-granular zone of adult hippocampus [40]. Continuous exposure to social defeat stress in the resident/intruder model induces anxiety-related and not anhedonia-like phenotypes. The dorsal hippocampus in these rats has elevated BMP4 and phosphorylated SMAD1/5/9 expression, and decreased neurogenesis [43] (Fig 1).

Disruption of dorsal hippocampal neurogenesis catalyzes aberrant emotional behavior including, anxiety [44, 45], which results in a loss of efficient integration of novel information, amplification of negative associations and exaggerated response to aversive cues [46]. Overall these findings indicate that the TGF-β family of proteins provide allostatic control of neurogenesis and affective behavior through a positive and negative feedback loop mediated by activin A and BMP signaling, respectively. Additionally, the role of TGF-β signaling and affective behaviors is increasingly being elucidated in other brain regions, such as the amygdala. Genetic variation in TGF-βR1 influences the association between amygdala volume and prenatal depression [47]. A study in mice has recently demonstrated that stress dampens the expression of Erbin, a neuronal adaptor protein, in the parvalbumin neurons of

the amygdala that may compromise Erbb2 signaling [48, 49]. Interestingly, Erbin interacts with TGF-β and could alter some of the resulting behavioral disturbances.

4. TGF-β signaling and Cocaine Use Disorder

Substance use disorder (SUD) such as cocaine use disorder (CUD) is a neuropsychiatric disease that is defined by a transition from voluntary recreational use of drugs of abuse to uncontrolled and compulsive drug-seeking habits [50–52]. During drug abstinence, an individual with SUD undergoes the transition to a negative emotional state and motivational 'withdrawal,' which are often characterized by persistent relapse vulnerability [51, 52]. Acute or chronic exposure to drugs of abuse leads to discrete cellular and molecular events in specific brain regions. The mesolimbic dopamine system governs reward and motivation and is the primary brain target of drug-induced cellular plasticity events underlying the vulnerability to drug use, abuse, and addiction phenotypes [53]. Such behavioral phenomena, characterized by a persistent craving for the drugs, is shared by both clinical populations, as well as preclinical models of substance use disorder. Preclinical models of addiction are generally based on motivated abstinence that allows for dissecting neuroadaptations underlying various endophenotypes, such as compulsive drug taking and perpetual relapse vulnerability [54]. Despite recent efforts, there remain few effective treatments for SUD. As the toll of this disease continues, it incurs a huge cost to our society, both socially and economically, and warrants a greater understanding of the molecular events underlying these maladaptive behaviors.

Decades of research have demonstrated that numerous molecular and cellular mechanisms purportedly underlie both short and long-term neuronal neuroadaptations following exposure to cocaine [55]. These discrete neuroplastic changes are mediated through dysregulated epigenetic [56], translational [57], ubiquitin proteasomal [58, 59], and spinogenetic [60] mechanisms.

4.1 TGF-β mediated neural adaptations in the Nucleus Accumbens

The nucleus accumbens (NAc) is a heterogeneous structure that forms the ventral striatum in the brain [61]. The NAc is a key brain region that is thought to be responsible for the integration of information from cortical and limbic regions to mediate reward-related behaviors. Within this brain region, 90% to 95% of the cell types are comprised of GABAergic medium spiny neurons that either express dopamine receptors (D1/D2) or neuropeptides. The remaining 5% to 10% of the neurons are neuropeptide-expressing interneurons [61–64]. Such topographical heterogeneity positions the NAc as a critical region for regulating appetitive and motivated behaviors [61, 65–67]. Neuroadaptations in the NAc are thought to serve as the molecular basis of relapse vulnerability and pathological motivation for drug seeking [61]. Prior studies have established that drugs of abuse produce constitutive changes in the NAc at the cellular and molecular levels that underlie addiction-related behavioral plasticity such as sensitization, learned associations, reinforcement, and compulsive relapse following abstinence [58, 59, 68–72].

4.1.1 Role of TGF-β in contingent versus non-contingent cocaine exposure

—Neurochemical determinants underlying addictive behavior vary based on the animal model employed. Neuroadaptations as a result of the motivational and cognitive processes

underlying active self-administration (contingent) differ when compared to animals receiving passive drug injections (non-contingent) [73]. Studies have demonstrated that contingent, when compared to non-contingent, cocaine exposure, mediates aberrant TGF-β signaling in the NAc. TGF-β receptor 1 (TGF-β R1) protein expression is potentiated in the NAc following abstinence from active, but not passive, cocaine exposure following 7 days of abstinence (AD7). This altered expression of TGF-β R1 in the NAc is not observed on AD7 after cocaine behavioral sensitization [74]. Though sensitization and self-administration involve overlapping neural circuitries, the precise neuroadaptations that drive persistent maladaptive plasticity underlying relapse from contingent versus non-contingent drug exposure vary [75]. The sensitization of incentive motivation is pivotal in dissecting addiction when compared to the sensitization of locomotion. Thus non-contingent cocaine exposure could sensitize the motor circuits, but not the neural substrates underlying motivation that is achieved through a more contingent self-administered paradigm [75]. Prior studies have demonstrated that non-contingent and contingent cocaine exposure elicits discrete long-term potentiation in the ventral tegmental area (VTA), a brain region central to motivational behaviors [76]. Similarly, calcium-permeable AMPA receptors and acetylcholine release are upregulated in the NAc following prolonged abstinence from active, and not passive, cocaine exposure, [77, 78] suggesting an analogous mechanism of action for drug-induced TGF-β signaling in the NAc.

4.1.2. Activin signaling promotes enduring behavioral plasticity—

Activin signaling is augmented in the NAc on AD7 compared to AD1 following cocaine self-administration. Such temporal activation in activin signaling is characterized by increased levels of phosphorylated activin receptor 2a and SMAD3 [79]. At the pharmacological level, intra-NAc microinjection of activin A potentiates within-session cocaine dose-response, whereas activin receptor antagonist SB-431542 attenuates this behavior [79]. Further, viral-mediated overexpression of the dominant-negative form of SMAD3 blocks both within-session cocaine self-administration and cocaine-induced reinstatement. These findings suggest that SMAD3 signaling regulates both the rewarding properties of cocaine and associated relapse behavior (Fig 2).

Although extended access self-administration is typically utilized to model compulsive-intake behaviors, loss of controlled drug use can be better represented through a cocaine binge test during abstinence from self-administration [80]. The use of long-access cocaine taking in combination with a binge paradigm in animal models recapitulates the escalating dose binge cocaine phenomenon in human addicts and provides an additional model to understand the neurobiology of addiction [80–82]. Following a binge test on AD14, there is an upregulation of activin A levels in the NAc [83]. In such cases, the upregulated activin levels appear to be specific to microglia, the resident macrophages of the brain. Activin has been reported in multiple cell types [84], and the observed increase in activin A following a cocaine binge is only with respect to the microglial cell population when compared to neurons and astrocytes. Interestingly, there is accruing evidence of glia-mediated synaptic alterations following exposure to drugs of abuse [84–91]. Studies have identified that activin signaling upregulates the production of inflammatory cytokine, IL-10 [92] and TNF-α triggers activin production in return [93]. Both TNF-α and IL-10 have a microglial origin and

are potentiated during cocaine exposure, [94] possibly explaining the role of activin in mediating synaptic reorganization and behavioral plasticity through cytokine programming. Additionally, activin interplays with brain derived neurotrophic factor (BDNF) in controlling the delicate balance between extra-synaptic and synaptic NMDARs that is essential for neuronal plasticity[95]. Recent studies have shown alcohol-induced over-representation of genes pertaining to TGF-β/SMAD3 receptor signaling in the brain [96] and a potentiated microglial NF-kB signaling [97] indicating overlapping inflammatory gene networks possibly linked with TGF-β pathways in the glial cells [98]. Thus, it can be presumed that perturbing activin signaling can dysregulate the intricate balance between cytokines and neurotrophic factors leading to changes in synaptic architecture attributed to drug-induced enduring behavioral adaptations.

4.1.3 Activin signaling influence cocaine-induced morphological plasticity—

Dendritic spines are multifunctional integrative units that form the basis of neuronal connectivity in the central nervous system [99]. The dynamic nature of the spines allows them to transition between several morphological and structural states in a short period of time [99]. Morphologically, dendritic spines are classified into stubby, thin, and mushroom spines [100]. In particular, the ratio of thin to mushroom spines is an indicator of dendritic plasticity. Increased numbers of mushroom-shaped spines are often suggestive of increased spine maturation, a mechanism underlying the strengthening of memories [101, 102]. Studies have indicated that exposure to drugs of abuse alters dendritic spine across various brain regions [69, 70, 103–106], and spine plasticity correlates with exposure to drug-associated cues and regulates relapse behaviors [106].

Activin signaling has been shown to modulate spine dynamics and influence synaptic plasticity [107–109]. Viral-mediated downregulation of SMAD3 results in modulation of nascent spines during abstinence in NAc medium spiny neurons characterized by alterations in the mushroom head diameter that correlate with cocaine-seeking behavior. These findings indicate that NAc canonical activin signaling fosters morphological and cellular plasticity underlying persistent relapse vulnerability [79]. Cocaine induced spine adaptations can selectively occur in D1 and D2 MSNs [110]. It is however unknown if SMAD-regulated transcriptional events influence spine dynamics in a cell-type specific manner and remains a key question under investigation.

4.2 TGF-β-mediated epigenetic programming underlying persistent neuroadaptations

4.2.1 Direct transcriptional control—

Vulnerability to the relapse-like state is modulated by convergent biological, environmental, and genetic factors. Epigenetics is defined as the regulation of heritable and reversible alterations in gene expression without direct changes to the DNA sequence [111]. Studies have demonstrated that epigenetic regulation is an integral component of TGF-β signaling via SMAD elements that have direct access to genomic components [29]. The upregulated R-SMADs (receptor regulated SMADs) comprise of two globular domains (referred to as the MHI and MHII) that are coupled through an unstructured linker. The hairpin structure of the MHI domain allows the R-SMADs to recognize specific nucleotide motifs, while the MHII domain recruits partner

proteins such as activators and epigenetic regulators, allowing spatio-temporal expression of target genes [29, 112, 113].

Upregulation of activin signaling in the NAc following abstinence to cocaine self-administration activates SMAD3 translocation to the nucleus [79]. This increased access to genomic elements allows augmentation of SMAD3 binding to promoters of *Ctnnb1* (β-catenin), *Grin2a* (Glutamate receptor subunit epsilon-1), *Mef2D* (Myocyte specific Enhancer Factor 2D), *Cap2* (Cyclase associated protein 2), and *Dbn1* (Drebrin) genes for regulating cocaine-induced neuroadaptations [79]. Studies have indicated that behavioral manifestations of cocaine-mediated neuroadaptations are the result of functional dysregulation of the β-catenin pathway in the NAc [114–118] (Fig 1). β-catenin is the transcriptional coactivator associated with the canonical Wnt signaling [119]. The non-canonical pathway involves activation of β-catenin independent Wnt signaling [120]. Wnt upregulation results in nuclear stabilization of β-catenin and its subsequent association, mainly with TCF/LEF family of transcription factors [121]. Such association allows β-catenin direct access to the chromatin remodeling machinery, enabling activation of a wide array of genes through histone acetylation [119, 122]. Several of these genes involve Wnt targets that have critical functionality in driving cellular homeostasis at morphological and structural levels [123–126]. Abstinence following cocaine challenge disrupts glutamate signaling in the NAc that is often characterized by a shift in AMPA and NMDA receptor ratios [68, 127–131]. The enhanced SMAD3 binding to the promoter for *Grin2b* following abstinence from cocaine exposure could explain the transcriptional relationship between activin signaling and glutamate receptor expression. Changes in glutamate signaling alter spine plasticity, possibly involving the actin cytoskeleton [69, 132, 133]. Actin dynamics are central to spine plasticity commonly observed with drugs of abuse [104, 134, 135]. Drebrin is an actin-binding protein that controls actin cycling and thereby influences dendritic spine plasticity positively, [136] which is a process tightly associated with robust transcriptional and epigenetic regulation [137, 138]. Interestingly, drugs of abuse can alter cellular mediators disparately thereby regulating the neuroadaptations essential for establishing enduring behavioral plasticity. Thus, the role of TGF-β pathways in the regulation of addiction-like behaviors across multiple drug classes remains an ongoing area of investigation.

TGF-β mediated transcriptional responses require chromatin remodeling, which can be governed by the association of ATP-dependent SWI/SNF chromatin remodeler, BRG1 on promoter sites. BRG1 forms a complex with SMAD3 [139], and recruitment of BRG1-SMAD complexes on gene promoters mediate TGF-β-dependent transcriptional events [139]. Following prolonged abstinence from cocaine self-administration, the interaction of BRG1 and SMAD3 is increased in the NAc in parallel with increased binding of BRG1 to promoters of SMAD3 target genes [83]. Intra-NAc microinjection of BRG1 inhibitor PFI3 decreases the interaction of BRG1 and SMAD3 and attenuates cue-induced reinstatement of cocaine-seeking. These behavioral and molecular events are replicated with the viral-mediated expression of a dominant-negative form of SMAD3 in the NAc, implying a concerted action of chromatin remodeling and SMADs for transcriptional programming underlying drug-induced neuroadaptations (Fig 1, 2). Dysregulation in chromatin remodeling complexes has been implicated in several psychiatric disorders. Mutations in matrix-associated, actin-dependent modulators of SWI/SNF chromatin proteins

are linked to schizophrenia, addiction, and autism [58, 140–142], whereas the ACF chromatin remodeling complex is involved in susceptibility to stress and addiction [143]. Further, there is emerging evidence for the role of chromatin remodeling in mediating drug-induced maladaptive neuroadaptations [58, 144–146]. The reporting of BRG1 in regulating cocaine-induced relapse behaviors bolsters further evidence for the role of TGF-β in modulating epigenetic plasticity underlying the addicted state.

4.2.2 Ubiquitin-mediated epigenetic control—

The ubiquitin-proteasome system (UPS) is comprised of ubiquitin ligases and proteasome structures governing synaptic and epigenetic plasticity [147, 148] events that are integral to memory consolidation and substance use disorder [149–151]. The UPS conjugates polyubiquitin tags to target proteins for identification and proteolysis through the 26S proteasome complex [147, 152]. E3 ubiquitin ligases (E3s) are a class of enzymes within the UPS system that coordinate ubiquitin conjugation [147, 152] and have gathered significant therapeutic interest for a variety of psychiatric disorders, [153] mainly due to their specificity for target proteins [154]. Disruption in the UPS mechanisms following exposure to cocaine has been demonstrated previously [155, 156]. SMAD ubiquitination-related factor 1 (Smurf1), Smurf2, and SCF/Roc1 are E3 ligases that are known to degrade SMADs. The Smurfs are of particular importance because SMADs recruit the Smurfs as part of their adaptor functions to various pathway mediators including the TGF- β receptor complex and the transcriptional components, and thereby mediate the degradation of these SMAD-associating proteins. Thus, Smurfs promote the fine control of signaling output by regulating the level of SMADs and other pathway mediators [157]. However, there is a limited understanding as to how ubiquitin mechanisms specific to TGF-β signaling are altered following exposure to drugs of abuse such as cocaine. Following prolonged, and not acute, abstinence from cocaine self-administration, BMP pathway intermediates SMAD 1/5 and pSMAD1/5 are upregulated along with the downregulation of their E3 ligase Smurf1 in the NAc. A reduction in Smurf1 reduces the degradation of SMAD1/5 leading to an increase in protein expression [59]. Activated pSMAD1/5 translocate into the nucleus for enhanced binding to promoters of *Egr3 (*Early growth response 3*), Dnml1 (*Dynamin-1 like protein*)* and *BRG1* genes, which have been shown to modulate cocaine-induced cellular and behavioral plasticity [59, 83, 158–160]. Moreover, overexpression of Smurf1 through viral-mediated gene transfer attenuates cue-induced cocaine-seeking, whereas expression of the catalytically inactive form potentiates it, establishing a bidirectional control of the TGF-β UPS system on cocaine-related behaviors. Hence, cocaine-induced neuroadaptations can involve hijacking ubiquitin mechanisms to control TGF-β pathways and associated transcriptional machinery (Fig 1, 2).

5. Hippocampal plasticity and TGF-β signaling

Studies have established that the physiological effects of drugs of abuse are associated with contextual information [161, 162]. This association of drug-paired environmental stimuli forms maladaptive memories that are critical for the expression of relapse vulnerability. The hippocampus is the hub of synaptic reorganizations that play an essential role in facilitating contextual and declarative memories towards drug-induced behavioral outcomes

[21]. However, the role of the dorsal hippocampus in mediating relapse vulnerability during prolonged abstinence inflicted by drugs of abuse is sparsely explored.

The dorsal hippocampus activin A signals through the SMAD-independent non-canonical mechanism, rather than the SMAD-dependent canonical mechanism identified in the NAc, during prolonged abstinence (AD30), and activin signaling bidirectionally mediates cue-induced cocaine-seeking [163]. Activin A, which typically exhibits lower expression under basal conditions, is known to upregulate in response to increased neuronal activity [164], a phenomenon often integral to drug-induced neuroadaptations during incubation. Interestingly, activin A immunopositive microglial cells are upregulated in the NAc of the cocaine binge animals [83]. A similar expression profile for activin A is seen in both neuronal and microglial fractions obtained from the dorsal hippocampus in AD30 cocaine animals without any overall changes in neuronal and microglial immunoreactivity. This indicates that activin A signaling is steered exogenously by cocaine in both neurons and microglia in the dorsal hippocampus. Elevated activin A expression in microglia and neurons have been implicated in promoting synaptic reconfiguration through mechanisms shown to be regulated by addictive drugs such as cocaine [165]. These processes involve, and are not limited to, proliferation, oligodendrocyte differentiation, and myelination [166]. Pharmacological manipulation by endogenous activin signaling inhibitor, follistatin, or activin A antibody significantly reduces cue-induced seeking behavior. Conversely, viral-mediated overexpression of activin receptor 2A in the dorsal hippocampus potentiates cue-induced cocaine-seeking, thereby demonstrating bidirectional regulation of activin A in the dorsal hippocampus [163]. Prior research has reported that activin signaling impinges on conditioned responses that involve synaptic plasticity in the brain regions responsible for memory processing and execution [164]. Forebrain-specific overexpression of activin A following training for contextual fear conditioning in a transgenic mouse model results in strengthened reconsolidation of fear memory, whereas follistatin overexpression abrogates this effect [107]. Similarly, overexpression of the dominant-negative form of activin receptor 2a in forebrain neurons triggers low-anxiety behavioral phenotypes in exploration paradigms of anxiety behaviors [167]. This activin-mediated behavioral modulation involves synaptic organizations in brain regions such as the hippocampus leading to memory reconfiguration via altered glutamatergic signaling and long-term potentiation (LTP). Further, studies have also established SMAD-independent moderate long-term potentiation (LTP) via phosphorylation of GluN2B (p-GluN2B) [109]. Indeed, TGF-β promotes synaptic plasticity in rat hippocampal neurons [6], whereas activin is required for hippocampal LTP, consolidation of long-term memory, and induction of moderate LTP upon weak theta-burst stimulation by acting on NMDA receptor currents and spine density [109]. Increases in both p-GluN2B and LTP in the dorsal hippocampus of cocaine-treated rats compared with saline controls suggest that cocaine-induced activin A signaling in the dorsal hippocampus functions through GluN2B phosphorylation and altered synaptic plasticity. [163]. These findings further the understanding of the role of DH TGF-β signaling in cocaine-induced plasticity, establishing the importance of TGF-β proteins in memory reconsolidation and cellular plasticity required for augmented cocaine craving following prolonged abstinence (Fig 1, 2).

6. Future perspective

TGF-β family of proteins have diverse cellular and temporal functionality, making them an obvious choice for investigation in various diseases including addiction and affective conditions [47, 168, 169]. However, the current knowledge on TGF-β signaling and psychiatric disorders is largely unexplored. There is supportive evidence from clinical studies of the role of Activin signaling in modulating antidepressant response [20] and cross-sectional study on CUD patients exhibit altered TGF-β plasma levels when compared to control group [169]. Further, sex differences in TGF-β signaling with respect to various pathological domains of psychiatric and inflammatory conditions have been reported [170, 171]. Studies in peripheral systems have revealed that sex hormones can influence TGF-β signaling. Female sex hormone estrogen can induce BMP2/6 transcription and Smad2/3 degradation through proteasomal pathways [172, 173]. Male sex hormone testosterone has also been shown to modulate the expression of several TGF-β pathway mediators [174]. The role of sex hormones in influencing TGF-β signaling that may underlie neuropsychiatric disorders remains to be determined and remains under investigated. Clearly, the relative dearth of studies using female subjects has hindered a more complete understanding of the neurobiology of neuropsychiatric disorders [175]. Understanding how sex hormones modulate the neuroadaptations will be critical in revealing sex specific effects underlying these disorders.

Further, region specific changes in TGF-β pathways discretely influence neuroadaptations. For example, repeated cocaine exposure results in dynamic changes in the prefrontal cortex transcriptome with differentially enriched TGF-β pathways [176]. Moreover, the TGF-β family of proteins are produced in various cell types and can function distantly from their site of release, making them an ideal cross-talk candidate across diverse cells and brain regions. There is also little to no understanding of the discrete mediators within the canonical (different SMAD types) and non-canonical (various kinases) signaling cascades and how they can shape a diverse set of plasticity events. Overall, there remains a huge scope of investigating as to how these pathways diverge based on sex, cell type and region differences in the brain to regulate cellular plasticity underlying psychiatric disorders. Here we provide a detailed understanding of various components of the TGF-β signaling pathways rewiring critical neural substrates underlying behavioral plasticity through epigenetic, translational, and morphological adaptations. We also summarize how the loss of intricate balance in the TGF-β pathways can lead to affective behaviors. We believe this will promote novel avenues for effective therapeutic intervention targeted at combating these disorders.

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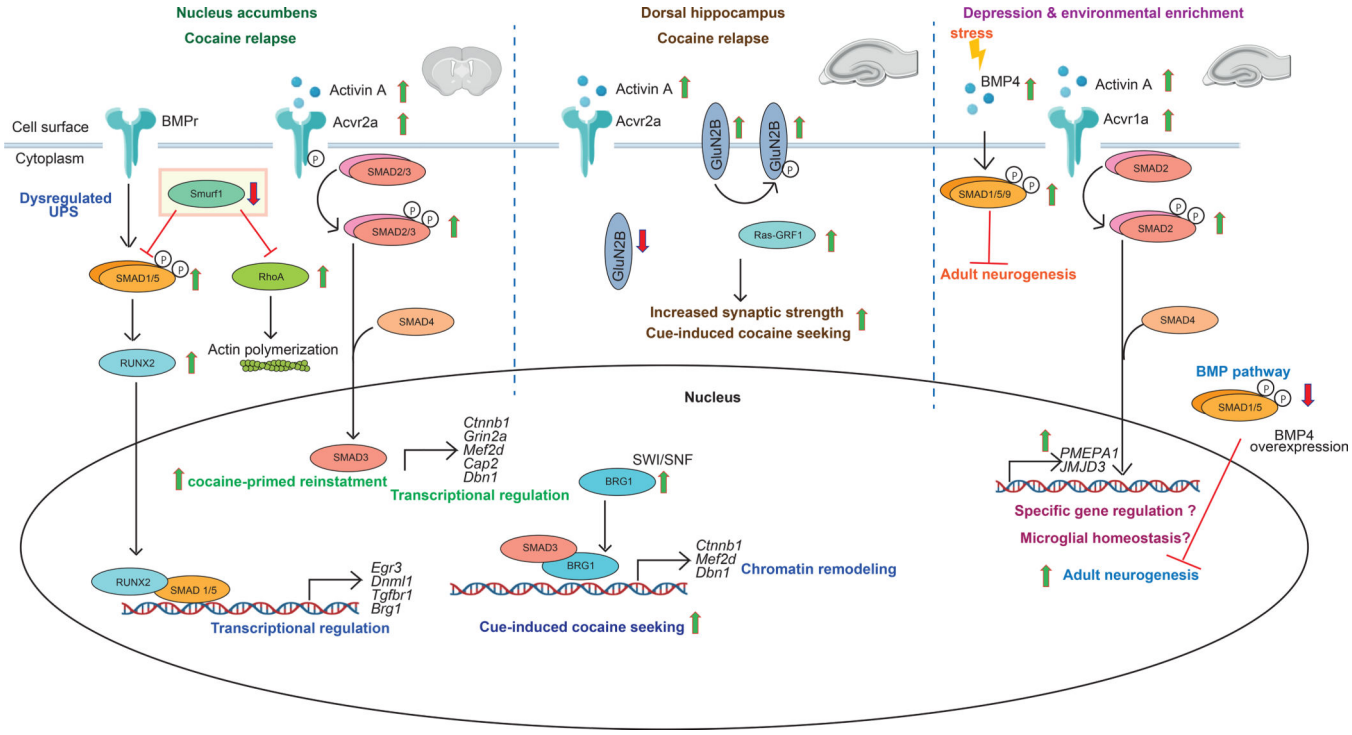

Figure 1:

The TGF-β family of proteins mediates brain region-specific divergent neuroadaptations involving dysregulated ubiquitin proteasomal system, abnormal chromatin remodeling, and altered transcriptional and synaptic mechanisms underlying cocaine-induced plasticity. At abstinent day 7 from extended access cocaine self-administration the canonical transcriptional activin A signaling is elevated in the nucleus accumbens that results in potentiated SMAD3 phosphorylation. Increased phosphorylation leads to altered SMAD3-mediated spine remodeling and transcriptional programs that is thought to be mediated through recruitment of chromatin remodeler BRG1. On the contrary, a similar abstinent time point following short access to cocaine potentiates the BMP pathway in the nucleus accumbens through increase in SMAD1/5 phosphorylation. An elevated SMAD1/5 level is attributed to reduced expression of its proteasomal regulator SMURF1 and increased expression of transcription factor RUNX2 that initiates unique transcriptional changes. At AD30 from cocaine self-administration, activin A non-canonical signaling is increased in the dorsal hippocampus where RAS-GRF1 is increased concomitant with increased levels of p-GluN2B and altered synaptic plasticity. Canonical activin A pathway via SMAD2 is elevated while BMP pathway intermediates SMAD1/5 is decreased in hippocampus of rodents treated with anti-depressants, environmental enrichment and electroconvulsive stimulation. This potentiated activin A signaling in the hippocampus leads to altered neurogenesis and transcriptional plasticity involving PMEPA1 and histone demethylase, JMJD3. Exposure to stress activates the BMP pathway through SMAD 1/5/9 that morphologically blocks neurogenesis. Abbreviations: TGF-β: Transforming growth factor β; SMAD: ((Caenorhabditis *elegans* SMA (“small” worm phenotype) and MAD family (“Mothers Against Decapentaplegic”)); BMPr: Bone morphogenetic protein receptor; Acvr2a: Activin receptor 2a; Acvr1a: Activin receptor 1a; RUNX2: Runt-related

transcription factor 2; RhoA: Ras homology family member A; Ras GRF-1: Ras-specific guanine nucleotide-releasing factor 1; GluN2B: Glutamate [NMDA] receptor subunit epsilon-2; BRG1: Brahma-related gene-1; PMEPA1: Prostate Transmembrane Protein, Androgen Induced 1; JMJD3: Jumonji Domain Containing 3; BMP4: Bone morphogenetic protein 4.

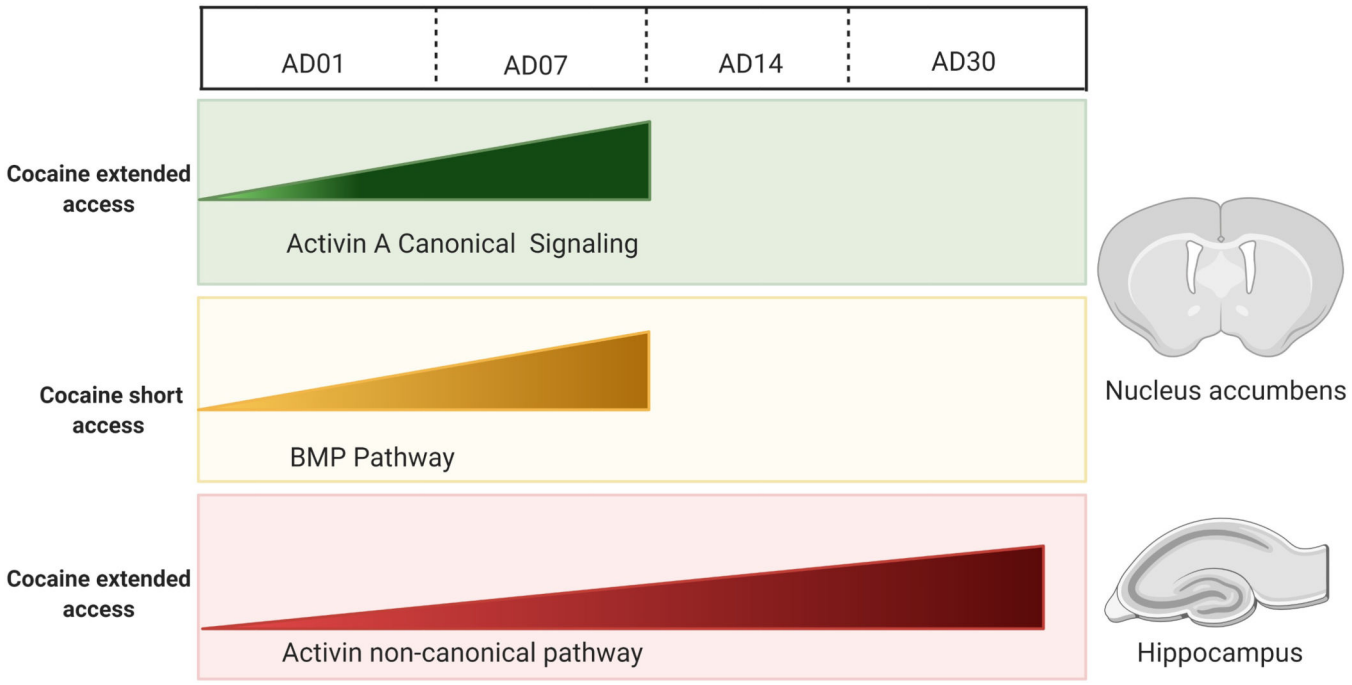

Figure 2:

Temporal functionality of TGF-β family of proteins across neural substrates underlying cocaine-induced plasticity. Activin-mediated canonical SMAD signaling is potentiated in the nucleus accumbens at AD07 when compared with AD01 in animals that undergo extended access cocaine self-administration. On the contrary, extended access regimen elevates activin-mediated non-canonical signaling in the dorsal hippocampus. A short-access cocaine self-administration potentiates the bone morphogenetic protein (BMP) pathway at AD07 when compared with AD01. Abbreviations: AD07: Abstinence day 7; AD01: Abstinence day 1.

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Table 1:

Brain region specific diverse role of TGF-β family of proteins in models of neuropsychiatric disorders.

Ligand	Receptors	Signaling mediator	Neuropsychiatric disorder	Role in plasticity	Neuroadaptations	Brain region	References
Activin	Acvr1a	SMAD2/3	Depression	i) Anti-depressants/ Electroconvulsive stimulation/ environmental enrichment in rodents increase Activin signaling involving Acvr1a and SMAD2 and reduce depression-like behavior. SMAD2 is increased in clinical responders to anti-depressants while SMAD3 is decreased in non-responders.	Enhanced neurogenesis. Possible epigenetic changes.	Dorsal hippocampus	[20], [29], [30], [31], [32], [31]
BMP	N/A	SMAD 1/5	Depression	BMP signaling is downregulated by antidepressants.	Reduced neurogenesis	Dorsal hippocampus	[39]
Follistatin	N/A	N/A	Anxiety	Overexpression of Follistatin in the forebrain influence synaptic changes and induce anxiety-like phenotypes.	Reduced neurogenesis	Hippocampus	[40]
BMP4	N/A	SMAD1/5/9	Stress-induced	Repeated exposure to social defeat stress potentiate BMP4 pathway involving SMAD1/5/9 with anxiety-related phenotypes.	Reduced neurogenesis	Dorsal hippocampus	[43]
TGF-β	TGF-βRIA	N/A	Cocaine Use Disorder	Increased TGF-βIR expression following abstinence (AD7) from cocaine SA.	N/A	Nucleus accumbens	[74]
Activin	i) AcvR2a ii) N/A iii) AcvR2a	i) SMAD3 (canonical) ii) N/A iii) RAS-GRF- p-GluN2B (non-canonical)	Cocaine Use Disorder	i) Increased Activin signaling at AD7 following cocaine SA. Blocking Activin signaling attenuates within session cocaine SA and cocaine-induced reinstatement. ii) Cocaine binge following SA at AD14 potentiated Activin A signaling. iii) Activin A signaling is increased at AD30 following cocaine SA. Modulating Activin A signaling bidirectionally regulates cue-induced cocaine seeking.	i) Epigenetic and morphological plasticity. I i) Altered glial dynamics through microglial activation. iii) Translational and synaptic plasticity.	Nucleus accumbens Nucleus accumbens Dorsal hippocampus	[79] [83] [119]
BMP	N/A	SMAD 1/5/8	Cocaine Use Disorder	BMP pathway is elevated via SMAD 1/5/8 at AD7 following short access cocaine SA and	Ubiquitin proteosomal mediated epigenetic plasticity involving smurf1 and Runx2.	Nucleus accumbens	[59]
TGF-β	N/A	SMAD3	Alcohol dependence	Overrepresentation of TGF-β/SMAD3 pathway genes specific to microglia.	Overlapping glial and inflammatory networks	Whole brain/PFC	[96], [97]. [98]