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Epigenetic mechanisms of rapid-acting antidepressants

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BACKGROUND: Rapid-acting antidepressants (RAADs), including dissociative anesthetics, psychedelics, and empathogens, elicit rapid and sustained therapeutic improvements in psychiatric disorders by purportedly modulating neuroplasticity, neurotransmission, and immunity. These outcomes may be mediated by, or result in, an acute and/or sustained entrainment of epigenetic processes, which remodel chromatin structure and alter DNA accessibility to regulate gene expression.
METHODS: In this perspective, we present an overview of the known mechanisms, knowledge gaps, and future directions surrounding the epigenetic effects of RAADs, with a focus on the regulation of stress-responsive DNA and brain regions, and on the comparison with conventional antidepressants.
MAIN BODY: Preliminary correlative evidence indicates that administration of RAADs is accompanied by epigenetic effects which are similar to those elicited by conventional antidepressants. These include changes in DNA methylation, post-translational modifications of histones, and differential regulation of non-coding RNAs in stress-responsive chromatin areas involved in neurotrophism, neurotransmission, and immunomodulation, in stress-responsive brain regions. Whether these epigenetic changes causally contribute to the therapeutic effects of RAADs, are a consequence thereof, or are unrelated, remains unknown. Moreover, the potential cell type-specificity and mechanisms involved are yet to be fully elucidated. Candidate mechanisms include neuronal activity- and serotonin and Tropomyosine Receptor Kinase B (TRKB) signaling-mediated epigenetic changes, and direct interaction with DNA, histones, or chromatin remodeling complexes.
CONCLUSION: Correlative evidence suggests that epigenetic changes induced by RAADs accompany therapeutic and side effects, although causation, mechanisms, and cell type-specificity remain largely unknown. Addressing these research gaps may lead to the development of novel neuroepigenetics-based precision therapeutics.

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INTRODUCTION

Chromatin is a plastic entity, which adapts to external stimuli such as a changing environment and stress [1, 2]. This feature shapes the endogenous response to a changing environment via long-term modulation of gene expression [3, 4]. Psychosocial stress causes an epigenetic remodeling of stress-responsive DNA and chromatin regions, and associated histone proteins in susceptible brain areas such as the ventral hippocampus [1, 5], amygdala [6], nucleus accumbens (NAc) [7], and the prefrontal cortex (PFC) [8] – dorsal raphe nucleus loop [9–11]. Similarly, and in an opposite fashion, a remodeling of chromatin regions involved with synaptic plasticity, neurotransmission, neurogenesis, and neuroinflammation is required in infralimbic and prelimbic neurons to elicit antidepressant effects [1, 9–13]. Hence, drugs which directly or indirectly affect the epigenetic control of chromatin regions linked to neurotransmission, neurogenesis, and neuroinflammation, represent promising epigenetics-based therapeutics.

Rapid-acting antidepressants (referred herein as RAADs) are being investigated as novel therapeutics in psychiatry [14–16]. These compounds are generally classified as serotonin $(5\text{-HT})_{2A}$ receptor agonists such as psilocybin, lysergic acid diethylamide (LSD), N, N-Dimethyltryptamine (DMT) and 2,5-Dimethoxy-4-iodoamphetamine (DOI) [14]; N-Methyl-D-Aspartate (NMDA) antagonists such as ketamine [17]; and empathogens such as 3,4-methylenedioxymethamphetamine (MDMA), which act mainly through neurotransmitter transporters [18]. The long-term improvements in psychiatric symptoms and neuropsychological function elicited by RAADs [19–24] are accompanied by enduring serotonergic (such as a peripheral increase of serotonin -5-HT- platelets uptake sites in long-term Ayahuasca users) [25], and neuromorphological changes (such as thinner precuneus and posterior cingulate cortex and thicker anterior cingulate cortex in long-term Ayahuasca users) [26], which suggest the entrainment of epigenetic mechanisms.

Preliminary evidence indicates that the therapeutic effects of RAADs, akin to conventional antidepressants, are accompanied by a remodeling of DNA methylation, histone post-translational modifications (PTMs), and non-coding RNAs (ncRNAs) dynamics in stress-responsive brain areas. Interestingly, repeated, binge, or high-dose administration of RAADs elicit side effects mediated by overlapping yet opposite epigenetic mechanisms, such as hippocampal apoptosis, reduced neurotrophic signaling, increased neuroinflammation, and cognitive impairments (see Involvement of Epigenetic Mechanisms in Potential Side

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Effects Elicited by RAADs). These effects, contrasting with those of clinically relevant doses and resembling stress-induced epigenetic responses, underscore the importance of identifying the optimal dosages and regimens for clinical RAADs applications to maximize desirable epigenetic outcomes and minimize undesirable ones.

EPIGENETIC CONTROL IN STRESS-RELATED DISORDERS, AND THE EFFECTS OF CONVENTIONAL AND RAPID-ACTING ANTIDEPRESSANTS

DNA methylation, stress, and rapid-acting antidepressants

DNA methylation consists in the reversible addition of methyl groups to cytosines in CpG dinucleotides by DNA methyltransferases (DNMTs). This modification generally modulates transcription by inhibiting the binding of transcription factors or recruiting proteins involved in gene repression [27]. Stress and psychosocial trauma modulate the methylation status of CpG dinucleotides in DNA sequences involved with the stress response, and synaptic and neuronal plasticity [28–43]. For example, the methylation status of genes encoding the glucocorticoid receptor, arginin-vasopressin, and the brain-derived neurotrophic factor (BDNF) can be modulated by early-life adversities as early as 1 day after birth [28–43] and specific cell types such as astrocytes carryover the epigenetic marks of stress [35, 44]. Epigenetically-active compounds with DNA demethylase activity [45] have antidepressant effects [46, 47], confirming that the methylation state and the associated psychiatric symptoms can be reversed pharmacologically [48]. Stressors also affect the regulation of DNA-methylating enzymes such as DNMT3a and 3b [49] in stress-susceptible brain areas such as the PFC and hippocampus [35, 44, 50]. Therefore, stress exposure is physically "remembered" in specific cell types and brain areas, causing altered gene expression and ultimately lasting effects on behavior. The most studied example of epigenetic programming by stress, and its normalization by antidepressants, is the BDNF gene. Prenatal and life adversities decrease the promoter IV-mediated BDNF expression via increasing its methylation [36, 43, 49, 51–58], and psychiatric disorders largely share increased BDNF promoter methylation, which can be reversed by conventional antidepressants [36, 54–61].

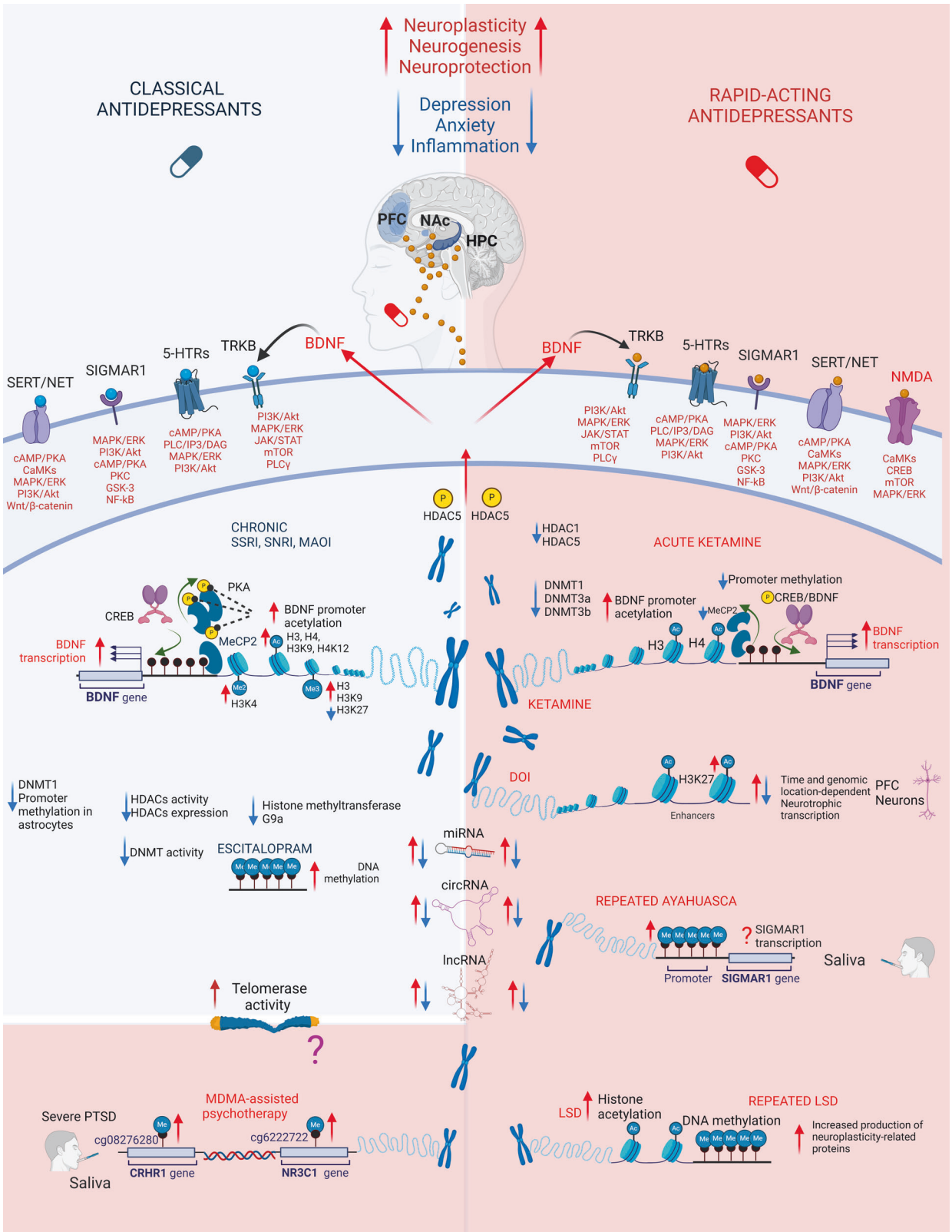
Like conventional antidepressants, but only requiring one or few administrations, ketamine restores some of the stress-induced aberrant DNA methylation, including on the BDNF gene (Fig. 1 and Table 1). Delving into the molecular mechanisms, ketamine induces a Extracellular Signal-Regulated Kinase 1 (ERK1) / nuclear receptor binding protein 1 (NRBP1)-mediated microglial decrease of methyl-CpG binding protein 2 (MeCP2), which upregulates the cAMP response-binding protein (CREB)-mediated BDNF exon IV transcription [62]. The enhancement of fear extinction elicited by ketamine is also accompanied by demethylation of PFC and hippocampal BDNF exon IV, and increased BDNF transcription [49]. Similarly, fluoxetine dissociates the MeCP2–CREB complex from BDNF promoter IV through the protein kinase A (PKA)-mediated phosphorylation of MeCP2, thus increasing BDNF transcription [55]. Resembling chronic imipramine's effects in the PFC [50], acute ketamine reversed the nerve injury-induced increase in the hippocampal DNMT1, 3a, and 3b. It also restored the decrease in hippocampal total BDNF and BDNF exon I transcription and protein levels [52]. In rodents, chronic fluoxetine, imipramine, and desipramine blunted the stress-induced increase in hippocampal DNA methylation, and restored the decrease elicited in the PFC [50, 63, 64]. Antidepressant use increased the peripheral methylation level of the 5-HT transporter [65], and the interleukin (IL)-6 gene [66], as well as telomerase activity in individuals with PTSD [67]. While it has been speculated that RAADs such as psilocybin might increase telomerase activity and telomere length, this hypothesis remains to be tested [68].

Amongst psychedelics, preliminary evidence indicates that LSD and Ayahuasca affect DNA methylation (Fig. 1 and Table 1). Repeated LSD largely increased the methylation level of 635 CpG sites in the PFC of adult male mice receiving a prosocial, anxiolytic, and synaptoplastic repeated regimen of LSD [69–72]. The genes interested were involved with neurotropic-, neurotrophic-, and neuroplasticity-related signaling. Proteomics profiling and qRT-PCR validation suggested specificity and functional significance of the changes observed in DNA methylation [69]. Given that cytosine methylation can affect the likelihood of mutations [73, 74] future studies are warranted to investigate the potential effects of the increased DNA methylation elicited by LSD on genomic stability and mutation rates. Despite the fact that the use of RAADs has been associated with decreased likelihood of suicide [75, 76], DNA hypermethylation is also observed in the blood of individuals who attempted suicide [77] and in the PFC of suicide completers [78]. Hence, future studies are required to better characterize the relationships between the epigenetic effects elicited by psychedelics and suicidality. Participation in a ceremonial Ayahuasca retreat in the Amazon consisting of multiple administrations increased the saliva methylation level of 5 CpG sites within the Sigma-1 receptor gene promoter (in a greater fashion in individuals with greater childhood trauma), but did not affect the methylation level of one CpG site within the FKBP5 gene, which is involved with trauma and the stress response [79]. These changes were accompanied by improved depression and anxiety scores for up to 6 months [79]. While they are preliminary findings, previous biochemical and neurostructural evidence supports the existence of epigenetic mechanisms accompanying the regular consumption of Ayahuasca: increased platelets 5-HT uptake sites [25], thinner precuneus and posterior cingulate cortex, and thicker anterior cingulate cortex [26] were identified in long term Ayahuasca users. Speculations exist that Ayahuasca might extinguish the fear response via an epigenetic mechanism mediated by the DMT-activated Sigma-1 receptor [80], although this hypothesis remains to be tested. The β-carbolines contained in the Ayahuasca brew might also inhibit histone deacetylase activity, given that engineered derivatives containing β-carbolines motifs are potent HDACs inhibitors [81, 82]. However, no studies have insofar investigated the epigenetic effects elicited by β-carboline, or those elicited by the combination of β-carboline with DMT-containing plants (as in the case of Ayahuasca).

MDMA-assisted psychotherapy led to peripheral epigenetic changes correlated to therapeutic improvement [83]. The increase in saliva methylation level of one CpG site (cg08276280) in the corticotropin-releasing factor receptor 1 gene and one (cg01391283) within the glucocorticoid receptor gene was correlated with symptom reduction in individuals with severe PTSD receiving MDMA-assisted psychotherapy [83]. Further studies should characterize the epigenetic effects of psychotherapy coupled to RAADs, and if those treatments synergistically or additively interact to produce determinate epigenetic outcomes. Putative prophylactic or acute effects of RAADs on attenuating stress-induced DNA methylation changes remain to be elucidated.

Histone post-translational modifications, stress, and RAADs

Histones form protein cores around which DNA wraps. Stress and antidepressants affect histone post-translational modifications (PTMs) such as acetylation, methylation, and phosphorylation in stress-responsive chromatin areas, altering chromatin accessibility and transcription. For example, stress elicits hypoacetylation of hippocampal histone 3 (H3) at BDNF III and IV promoters, and increases the levels of histone deacetylases (HDACs) including HDAC5 and Sirtuin 2, ultimately decreasing BDNF expression [1, 84]. Indeed, specific HDACs such as HDAC2 and HDAC5, which are critical regulators of adult neurogenesis [85] and cognition [86], are altered in depression [87].



Some of the aberrant PTMs dynamics elicited by stress are restored by chronic administration of conventional antidepressants such as fluoxetine, paroxetine, reboxetine, citalopram, imipramine and mirtazapine. These drugs rescue the H3-H4 (i.e., H3 lysine (K)9 and H3K27) hypoacetylation of the BDNF promoters, reverse the stress-induced decrease in BDNF transcription and protein level, promote HDAC5 phosphorylation and nuclear export, and attenuate the stress-induced increase in HDACs in

Fig. 1 Converging epigenetic mechanisms of rapid-acting and conventional antidepressants. Abbreviations: 5-HTRs, Serotonin Receptors; SIGMAR1, Sigma-1 Receptor; SERT, Serotonin Transporter; NET, Norepinephrine Transporter; TRKB, Tropomyosin Receptor Kinase B; BDNF, Brain-Derived Neurotrophic Factor; NMDA, N-Methyl-D-Aspartate; PLC, Phospholipase C; IP3, Inositol trisphosphate; DAG, Diacylglycerol; MAPK, Mitogen-Activated Protein Kinase; ERK, Extracellular Signal-Regulated Kinase; PI3K, Phosphoinositide 3-Kinase; Akt, AKT Serine/Threonine Kinase 1; PKC, Protein Kinase C; GSK-3, Glycogen Synthase Kinase 3; NF-kB, Nuclear Factor Kappa-B; CaMKs, Calcium Calmodulin Dependent Protein Kinases; Wnt, Proto-Oncogene Wnt-1; JAK, Janus Kinase; STAT, Signal Transducer and Activator of Transcription; PLCγ, Phospholipase C Gamma 1; SSRI, Selective Serotonin Reuptake Inhibitors; SNRI, Serotonin-Norepinephrine Reuptake Inhibitors; MAOI, Monoamine Oxidase Inhibitors; H3, Histone 3; H4, Histone 4; H3K4, Histone 3 Lysine 4; H3K9, Histone 3 Lysine 9; H3K12, Histone 3 Lysine 12; H3K27, Histone 3 Lysine 27; PKA, Protein Kinase A; Mecp2, Methyl-Cpg Binding Protein 2; CREB, cAMP Response Element-Binding Protein; G9a, Histone Methyltransferase G9a; HDAC, Histone Deacetylase; DNMT, DNA Methyltransferase; lncRNA, Long non-Coding RNA; circRNA, Circular RNA; miRNA, micro RNA; NR3C1, Glucocorticoid Receptor; CRH31, Corticotropin Releasing Hormone; PTSD, Post-Traumatic Stress Disorder; LSD, lysergic acid diethylamide.

stress-susceptible brain areas [1, 55, 84, 88–92]. Delving into the mechanisms, fluoxetine was shown to disassociate the MeCP2-CREB-BDNF promoter IV complex via Protein Kinase A (PKA)-mediated phosphorylation of MeCP2, leading to CREB-mediated BDNF transcription [55]. Fluoxetine also inhibited the binding of delta-FosB to the Calcium/calmodulin-dependent protein kinase IIa (CaMKIIa) promoter by reducing its acetylation and increasing its H3K9 dimethylation, ultimately decreasing CaMKIIa expression in the NAc [93]. Eight-week escitalopram treatment in individuals with depression decreased H3K27 histone trimethylation, and these changes were negatively correlated with increased BDNF levels [58]. Importantly, the stress-induced hippocampal BDNF promoter-associated H3K9 hypoacetylation and HDAC2 over-expression can also be restored by non-pharmacological strategies such as acupuncture [94].

The epigenetic outcomes elicited by a single administration of ketamine largely overlap those elicited by chronic conventional antidepressants. Indeed, one or few ketamine administrations are sufficient to reverse the stress-induced histone hypoacetylation and downregulated neurotrophic-related transcription (Fig. 1 and Table 1). In a mouse model of Gulf War Illness, ketamine decreased the hippocampal HDAC1 and HDAC5 levels and increased the H3K9 acetylation of BDNF promoter IV, restoring BDNF levels and neuroplasticity [95]. Similarly, in rats exposed to early life adversities, ketamine decreased the depressive-like behaviors and restored NAc HDAC activity [7]. Moreover, high-dose ketamine had a prophylactic effect on attenuating the stress-induced increase in hippocampal H3K9 methylation [96]. Similarly to conventional antidepressants, ketamine increases HDAC5 phosphorylation and nuclear export, resulting in enhanced H3-H4 acetylation. This triggers the myocyte enhancer factor 2-mediated transcription of the plasticity-related genes Eukaryotic Translation Initiation Factor 4E Binding Protein 1 (eIF4EBP1) and CREB, and their target genes, and ultimately the onset of antidepressant-like effects [97].

Psychedelics such as LSD and DOI also have histone-acetylating properties, which might be involved in their therapeutic effects (Fig. 1 and Table 1). Early studies reported that LSD acutely increases histone acetylation in the midbrain and cortex, but not the cerebellum of rabbits [98]. The increased histone acetylation activity elicited by LSD suggests gene activation, and indeed, LSD activates the transcription [99] of immediate early genes and genes involved with synaptic potentiation and neurotropism in the hippocampus, cortex, midbrain [100], and brainstem [99]. Given that enhancing hippocampal and PFC histone acetylation ameliorates fear extinction [101] and the consolidation of cued fear extinction [102] via a permissive effect over transcription [101], the increased histone acetylation elicited by LSD could be involved in its therapeutic action for alcohol addiction, and distress associated with a life-threatening condition [103–106].

A single administration of the LSD analog DOI also elicited a sustained modulation of the acetylation level of the transcriptional enhancer histone H3K27 in neurons of the mouse PFC [107]. This sustained effect had highly specific spatio-temporal dynamics, was accompanied by neurotrophic-related transcriptional shifts, and was associated to enhanced synaptic plasticity and antidepressant-like activity [107]. Lastly, the recently identified histone PTMs serotonylation and dopaminylation [108–110] might potentially be involved in the therapeutic effects of psychedelics, although further investigations are required. Together, the therapeutic effects of RAADs, similarly to conventional antidepressants, are accompanied by PTMs opposite to those elicited by stress, leading to increased accessibility of genes involved with neurotrophic signaling and antidepressant response.

Non-coding RNAs, stress, and RAADs

Non-coding RNAs (ncRNAs) are portions of the genome which are transcribed but not translated, with roles in tissue-specific selective or cooperative regulation of splicing, transcription, and translation [111–114]. ncRNAs, including stress-responsive ones, are intricately linked to neuroplasticity, psychiatric disorders, and suicide, offering potential as biomarkers and therapeutics for psychiatric disorders [115–122]. Early-life and chronic stressors affect the PFC, amygdalar and hippocampal regulatory RNA network, influencing neurotransmission, neuroplasticity, neurogenesis, and behavior [118, 123–127]. Among these networks, microRNAs (miRNAs), approximately 22 nucleotides in length, stand out for their tissue-specific regulation of a significant proportion of protein-coding genes expression by binding mRNA untranslated regions. Dysregulated miRNA dynamics are observed in depression and suicide, with studies pinpointing alterations in the PFC and hippocampus during depressive states [121, 122, 128, 129]. Conventional antidepressants influence miRNA expression patterns. For instance, miRNAs such as miR-16, miR-124, miR-132, and miR-135 are implicated in antidepressant response, with drugs like fluoxetine and venlafaxine, imipramine, sertraline, and citalopram modulating their expression, as well as the expression of miR-18a, miR-34a, miR-326, miR-1202 and miR-1971 [117, 130–141].

RAADs such as ketamine also alter miRNA pathways, with PFC miR-29b-3p, miR-98-5p, and miR-132-5p playing important roles in mediating the upregulation of BDNF leading to ketamine's antidepressant-like effects (Fig. 1 and Table 1) [142–144]. In preclinical studies, ketamine modulated some of the stress-dysregulated hippocampal miRNAs (i.e., miR-598), which are also regulated by other antidepressant strategies such as fluoxetine and electroconvulsive therapy (ECT) [124]. Ketamine also decreased miR-451 levels and increased those of the RNA-binding protein hur-6, a de-repressor miRNA "sponge" for deleterious miRNAs involved in inflammatory responses [124, 145, 146]. ECT and ketamine in rodents exposed to early-life adversities affected 43 common miRNA targets, 7 of which were reversals of stress-induced changes. Interestingly, ketamine rescued some of the stress-induced miRNAs alterations which were not reversed by fluoxetine [124], suggesting that some of the epigenetic mechanisms engaged by conventional and RAADs diverge. A three-day ketamine regimen upregulated 23 miRNAs and downregulated 15 including miR-206 [147] (a negative modulator of BDNF) in vivo

Table 1. Effects of rapid-acting antidepressant on DNA methylation, histone post-translational modifications, and ncRNAs.

STUDIES ON THE EPIGENETIC EFFECTS OF KETAMINE IN HUMANS		
Main findings	**Significance**	**Ref.**
The extent of decreases of the lncRNA FEDORA predicts the decrease in depression symptoms severity following a single ketamine administration in female (but not male) individuals with major depressive disorder (MDD)	The lncRNA FEDORA could be used as a marker of therapeutic response to ketamine in individuals who identify as female	[167]
An infusion of ketamine in individuals with treatment-resistant depression 24 hours after the first administration does not affect whole blood miRNA levels	Ketamine does not affect blood miRNA 24 hours after administration in individuals with treatment-resistant depression. The discrepancy from clinical findings might be due to the relatively small sample size, the fact that the samples were collected 24 hours after the first infusion, or the fact that whole blood was analyzed. Rapid-acting antidepressants might elicit cell type-specific miRNome fingerprints not detectable in whole blood	[162]
Deceased individuals that tested positive for ketamine have an acceleration in the mitochondrial epigenetic age of the nucleus accumbens and PFC	Ketamine abuse might accelerate the mitochondrial DNA epigenetic age	[216]
In clinical studies in individuals with neuropathic pain, ketamine differentially modulated miRNAs expression in responders and non-responders. The responder status could be predicted based on the lower pretreatment level of miR-548d-5p, which targets the UGT1A1 (UDP Glucuronosyltransferase Family 1 Member A1) gene	Ketamine elicits miRNA changes in individuals with neuropathic pain. Specific miRNAs could predict the therapeutic response to rapid-acting antidepressants	[160]
Poor responders to ketamine have considerable downregulation of circulating miR-605. Downregulating miR-605 leads to increased CXCL5 (C-X-C Motif Chemokine Ligand 5), and increased inflammation	miR-605-mediated regulation of CXCL5 predicted the treatment response to ketamine in complex pain regional syndrome	[161]
STUDIES ON THE EPIGENETIC EFFECTS OF KETAMINE IN ANIMALS		
Studies on the Effects of Ketamine on DNA Methylation in Animals		
Main findings	**Significance**	**Ref.**
Ketamine enhances fear extinction via decreasing the stress-induced hypermethylation of *Bdnf* (Brain-Derived Neurotrophic Factor) exon IV (involved with traumatic memory extinction). This effect is accompanied by increased exon IV and IX transcription in the medial prefrontal cortex (PFC) and hippocampus	The therapeutic effects of ketamine in post-traumatic stress disorder (PTSD), depression, and suicidality might be mediated at least partially by decreased *BDNF* promoter methylation leading to increased expression in the PFC and hippocampus	[49]
Ketamine elicits antidepressant-like effects via activating cAMP Responsive Element Binding Protein 5 (CREB)-mediated BDNF exon VI transcription, putatively in the PFC microglia. Ketamine decreases the levels of methyl-CpG binding protein 2 (MeCP2), a transcriptional repressor of BDNF	The synaptogenic and antidepressant effects of ketamine might be mediated at least partially via the epigenetic regulation of CREB-BDNF exon IV transcription in the PFC microglia	[62]
Ketamine reverses the increase in chronic pain-induced hippocampal mRNA and protein levels of the DNA methyltransferase (DNMT) 1, 3a, and 3b. Ketamine restores the chronic pain-induced decrease in total BDNF and BDNF exon I transcription and protein level. Ketamine normalizes the pain-induced increase in pro-BDNF mRNA and protein levels	The therapeutic effects of ketamine in chronic pain-induced depressive states might be mediated by a DNMT-mediated restoration of BDNF expression	[52]
Studies on the Effects of Ketamine on Histone Post-Translational Modifications in Animals		
Main findings	**Significance**	**Ref.**
Ketamine normalizes the stress-induced enhancement of adult nucleus accumbens histone deacetylase (HDAC) activity in a model of early-life stress, similarly to imipramine. Ketamine has no effect on PFC, hippocampal, and amygdalar HDAC activity	The therapeutic effects of ketamine on the pathophysiological sequelae of early-life stress might be partially mediated by a reduction of the stress-induced enhanced accumbal HDAC activity	[7]
Ketamine enhances HDAC5 phosphorylation at the sites S259 and S498 in a Ca^{2+} /Calmodulin-Dependent Protein Kinase II (CaMKII)- and Polycystic Kidney Disease (PKD)-dependent fashion in hippocampal neurons, leading to the cytoplasmic export of HDAC5, histones H3 and H4 acetylation, Myocyte Enhancer Factor 2 (MEF2)-mediated transcription, and Eukaryotic Translation Initiation Factor 4E Binding Protein (eIF4EBP) and CREB activation. Ketamine elicits a sustained (> 24 h) increase of HDAC5 phosphorylation in the hippocampus, and a sustained transcriptional modulation of MEF2-target genes (Activity Regulated Cytoskeleton Associated Protein *-Arc-*, Nuclear Receptor Subfamily 4 Group A Member 1 *-Nurr77-*, KLF Transcription Factor 6 *-Klf6-*, and Early Growth response 1 (*Egr1*). Blocking HDAC5 phosphorylation nullifies the antidepressant-like effects of ketamine	Ketamine-induced, AMPA-mediated enhanced hippocampal HDAC5 phosphorylation upregulates the cytoplasmic export of HDAC5 and this step is required to elicit antidepressant-like effects in rodents	[97]

Table 1. continued

Studies on the Effects of Ketamine on Histone Post-Translational Modifications in Animals		
Main findings	**Significance**	**Ref.**
Ketamine downregulates the increased HDAC1 and HDAC5 protein expressions in the hippocampus of rats elicited by Diisopropyl Fluorophosphate, and increases BDNF levels and dendritic spine density. Ketamine restores the decreased H3K9 acetylation of the BDNF promoter IV elicited by Diisopropyl Fluorophosphate	Ketamine elicits pro-histone acetylating effects and restores neuroplasticity in a mouse model of Gulf War Illness	[95]
Ketamine increases hippocampal BDNF promoter IV activity via HDAC5 phosphorylation at S259 and S498		
High-dose ketamine has a prophylactic effect on the stress-induced increase in hippocampal histone H3 lysine 9 (H3K9) methylation	Ketamine and potentially other rapid-acting antidepressants might have prophylactic effects against stress-induced epigenetic changes	[96]
Studies on the Effects of Ketamine on Non-Coding RNAs in Animals		
Main findings	**Significance**	**Ref.**
Ketamine increases miR-98-5p, but not miR-23a-5p and miR-3968 in the PFC and hippocampus of chronically stressed mice. miR-98-5p inhibition nullifies the antidepressant-like effects of ketamine	miR-98-5p upregulation is required for the antidepressant-like effects of ketamine	[143]
Ketamine modulates several hippocampal miRNAs, eliciting a decrease in miR-206 and miR-181a-5p (involved in apoptosis), and an increase in miR-132-3p and miR-29a-3p (involved in N-Methyl-D-Aspartate -NMDA- mediated neuronal survival and neurite remodeling). These effects are accompanied by a dose-dependent increase of BDNF levels in vivo and in vitro, and decreased apoptosis and electrical currents in hippocampal neuronal cultures	Ketamine-induced miRNA modulation decreases neuronal apoptosis and modulates the electrophysiological properties of hippocampal pyramidal neurons. The modulation of miR-206 by ketamine might be involved in its antidepressant effects	[147]
Ketamine and stress modulate hippocampal miRNAs (such as miR-598-5p, miR-451, miR-217, miR-203, miR-211, miR-152, miR-1, and miR-204) linked to pathways such as cAMP responsive element binding protein 5 (CREB5), GABAA, and muscarinic cholinergic receptor 5. Antidepressant effects of ketamine and electroconvulsive therapy converge on common molecular pathways (such as hippocampal miR-598-5p upregulation and miR-451 downregulation)	Ketamine and other antidepressant strategies modulate hippocampal miRNA pathways such as miR-451 which could be exploited in antidepressants drug-discovery	[124]
Ketamine administered to mice 6 hours prior to lypopolysaccharide (LPS) elicits prophylactic effects, putatively through normalizing the LPS-perturbed PFC expression of miR-149 (increased by LPS), and miR-7688-5p (decreased by LPS), and their target gene nuclear factor Nfatc4 (activated T cells 4, decreased by LPS). The expression level of miR-149 in the PFC negatively correlated to the relative abundance of the gut microbial genus *Alloprevotella*, while miR-7668-5p was positively correlated to the relative abundance of the latter, and negatively correlated to the relative abundance of *Lactobacilllus*	Ketamine elicits prophylactic effects in the PFC in response to a systemic inflammatory challenge. The PFC levels of selected miRNA affected by ketamine correlate to the abundance of specific gut microbiome taxa	[152]
Ketamine increases the hippocampal (but not PFC) transcription of a cluster of miRNAs (764-5p, 1912-3p, 1264-3p, 1298-5p, and 448-3p) hosted in the 5-HT_{2C} gene locus through Glycogen Synthase Kinase 3 (GSK-3). These effects on miRNA expression are not detected following acute or repeated treatment with the selective serotonin (5-HT) reuptake inhibitor (SSRI) fluoxetine. Blocking miR-448-3- decreases the antidepressant-like effect of ketamine	Hippocampal GSK-3-miR-448-3p signaling is required for the antidepressant-like effects of ketamine. Ketamine elicits a rapid and sustained modulation of hippocampal miRNA which is not shared with acute or repeated fluoxetine treatment and may contribute to its capacity to elicit antidepressant effects in individuals that do not respond to classical treatment	[150]
Ketamine increases miR-29b-3p expression and restores its expression in stressed mice selectively in the PFC, but not the hippocampus or the hypothalamus. While the miR-29b-3p target gene Glutamate Metabotropic Receptor 4 (GRM4) gradually declines following ketamine administration, the levels of miR-29b-3p increase. miR-29b-3p overexpression increases the high-voltage-activated current type in primary neuron cells, and promotes cell survival and cytodendritic growth	The brain area-specific effects of ketamine on miRNAs and their target genes (such as miR-29b-3p and GRM4) might be involved in its antidepressant effects.The synaptic-potentiating and neurotrophic properties of ketamine might be mediated by specific miRNAs in specific brain areas	[142]
Ketamine prophylactic treatment in chronically stressed mice affects the level of 32 miRNAs in the PFC; the miRNA with the most significant change (decrease) following ketamine is miR-132-5p, which targets the BDNF and Transforming Growth Factor Beta 1 (TGF-β1) genes, which are involved in the antidepressant effects of ketamine. Ketamine rescues the stress-induced decrease of BDNF and TGF-β1. Ketamine decreases the expression of Methyl-CpG Binding Protein 2 (MeCP2) in the PFC	Ketamine-induced miR-132-5p in the PFC and its resulting effects on gene expression plays an important role in the prophylactic antidepressant effects of ketamine, potentially through its regulatory effects on the expression of BDNF, TGF-β1, and MeCP2 in the PFC	[144]
Acute ketamine administration increases the PFC levels of miR-219a-5p, miR-7a-5p, miR-181b-5p and miR-148a-3p and decreases the levels of miR-128-3p. These miRNAs target genes involved with transcription, protein ubiquitination, and protein phosphorylation	Ketamine affects PFC miRNAs involved with transcription, and protein ubiquitination and phosphorylation in the PFC	[151]

Table 1. continued

Studies on the Effects of Ketamine on Non-Coding RNAs in Animals		
Main findings	**Significance**	**Ref.**
Repeated ketamine increases the hippocampal expression of the circRNAs 003460, 014900, 006565, 013109, and decreases circRNA-005442. The predicted downstream effects converge on calcium signaling, G protein signaling, protein phosphorylation, Mammalian Target of Rapamycin (mTOR) signaling, transcription, alternative splicing, and neuroplasticity	Ketamine modulates hippocampal circRNAs, and these effects might be involved in its antidepressant and neurotrophic effects	[164]
Ketamine decreases miR-214-3p and Glutathione Peroxidase 4 (GPX4) levels. miR-214-3p inhibition relieves the decreased GPX4 expression. Ectopic expression of long non-coding Pvt1 Oncogene (lncPVT1) reverses the suppressed GPX4 levels caused by ketamine. Ketamine elicits ferropoptosis	Ketamine might have hepatic antineoplastic effects at least partially through lncRNA PVT1/miR-214-3p/GPX4 signaling and ferropoptosis	[263]
STUDIES ON THE DELETERIOUS EPIGENETIC EFFECTS OF KETAMINE IN ANIMALS		
Main findings	**Significance**	**Ref.**
Repeated ketamine during early gestation decreases the cardiac histone H3K9 acetylation level at the Modulator Of VRAC Current 1 (Mlc2) promoter by increasing histone deacetylase activity, cardiac HDAC3 level, and the binding of HDAC3 at the Mlc2 promoter. This leads to cardiac enlargement, ventricular chamber enlargement, ventricular wall thinning, vacuolar degeneration of cardiomyocytes, reduced systolic function, and decreased expression level of several cardiomyogenesis-related genes	Repeated ketamine during early pregnancy elicits deleterious effects in the cardiac physiology of the offspring through its modulation of histone acetylation activity	[218]
Ketamine abuse induces Ten-Eleven-Translocation (TET) methylcytosine dioxygenase-mediated hypomethylation of NF-κB CpG promoter sites in cyclooxygenase 2 (COX2) promoters, upregulating COX-2. Ketamine upregulates (*permissive*) H3K4m3, and downregulates (*repressive*) H3K27me3 and H3K36me3 at NF-κB responsive COX-2 promoter sites, leading to ulcerative colitis	Epigenetic-mediated inflammatory dysfunction is involved in ketamine abuse-induced ulcerative cystitis. Low-dose ketamine might have a modulatory role over the epigenetic-mediated inflammatory control	[208]
Repeated high-dose ketamine leads to an upregulation of the circRNA circ-SFMBT2 which sponges and downregulates miR-224-5p, leading to increased Metadherin (MTDH) expression	circ-SFMBT2/miR-224-5p/MTDH signaling might be involved in the inflammatory dysfunction underlying ketamine-induced cystitis	[212]
In rats with ketamine-induced conditioned place preference (CPP), thirty-four hippocampal miRNAs were differentially expressed, including a strong downregulation of miR-331-5p, which targets the NR4A2 (Nuclear Receptor Subfamily 4 Group A Member 2) gene, and an increased expression of NR4A2, p-CREB, and BDNF	Hippocampal miRNAs might be involved in the rewarding and drug-seeking effects elicited by repeated ketamine exposure	[225]
Successful ketamine-induced CPP downregulates 122 miRNAs in the rat serum exosomes involved in processes such as nervous system development, neuron generation and differentiation, apoptotic processes, and pathways such as SNARE interaction, Protein Kinase CGMP-Dependent (PKG) signaling, and dopaminergic and GABAergic synapse. The downregulated miRNAs include miR-128-3p, 133a-3p, 152-3p, 181a-5p, 192-3p, 194-5p, 218b, 22-5p, 362-3p, 674-3p	Repeated ketamine exposure and CPP is accompanied by changes in serum exosomes miRNAs in rats	[231]
Repeated high-dose ketamine decreases miR-15a-3p, miR-15b-3p, and miR-16-1-3p expression in the PFC. Repeated high-dose ketamine decreases miR-16-1 in the hippocampus and Dopamine Receptor D1 (DRD1) levels in the PFC and hippocampus. These neurobiological changes are associated with schizophrenia-like behavior	Ketamine abuse may elicit maladaptive miRNAs expression in the PFC leading to schizophrenia-like behavior	[242]
Repeated high dose ketamine decreases miR-199a-5p expression and increases that of its target gene Hypoxia Inducible Factor 1 Subunit Alpha (HIF-1α). The regimen induces learning and memory impairment in neonatal rats through the regulation of the miR-199a-5p - HIF-1α pathways. Exposure to ketamine in neonatal rats induces learning and memory impairments. Exposure to ketamine impairs spatial learning memory ability by up-regulating HIF-1α expression	Repeated ketamine administration to neonates elicits cognitive and memory impairments through the miR-199a5p - HIF-1α pathway	[239]
miR-34c is upregulated in the hippocampus following repeated high-dose ketamine in neonatal rats. miR-34c knockdown increases the levels of BCL2 Apoptosis Regulator (Bcl-2), phospho-Protein Kinase C (PKC), and phospho-Mitogen-Activated Protein Kinase 1 (ERK). miR-34c knockdown ameliorates the ketamine-induced hippocampal toxicity Repeated high-dose ketamine elicits neurotoxicity in the CA1 region of the hippocampus	Repeated ketamine administration in the neonatal period elicits hippocampal neurotoxicity at least partially through miR-34c upregulation	[236]
miR-34a overexpression reverses the neurological and cognitive deficits, histopathological brain changes, and exacerbation of circulating proinflammatory cytokines elicited by repeated high-dose ketamine in rats	Repeated high-dose ketamine elicits neurotoxic and proinflammatory changes which can be counteracted by miR-34a overexpression	[213]

Table 1. continued

STUDIES ON THE DELETERIOUS EPIGENETIC EFFECTS OF KETAMINE IN ANIMALS		
Main findings	**Significance**	**Ref.**
Repeated high-dose ketamine decreases miR-214 and increases Phosphatase And Tensin Homolog (PTEN) expression in the hippocampus. Repeated high-dose ketamine elicits cognitive deficits in rats	Repeated high-dose ketamine elicits cognitive deficits in rats which might be due to decreased miR-214 and increased PTEN hippocampal expression	[240]
Repeated high-dose ketamine in the neonatal period downregulates hippocampal miR-137, leading to apoptosis in hippocampal CA1 neurons and significant long-term memory dysfunction. miR-137 overexpression protects against hippocampal neurodegeneration and memory loss	miR-137 is involved in the neonatal, repeated high dose ketamine-induced hippocampal neurodegeneration and memory loss	[238]
Chronic ketamine administration induces bladder fibrosis and bladder upregulation of 14 and downregulation of 9 miRNAs. Moreover, chronic ketamine administration leads to the upregulation of 37 and downregulation of 34 lncRNAs in the bladder. Additionally, the treatment leads to 14 downregulated and 54 upregulated circRNAs	The ketamine abuse-induced bladder fibrosis is accompanied by changes in ncRNAs in the bladder	[211]
Repeated ketamine administration increases histone deacetylase and DNA methyltransferase activity in the PFC and striatum, but not the hippocampus, eliciting hyperlocomotion and altered exploratory activity. Repeated ketamine administration decreases Nerve Growth Factor (NGF) and Glial Cell Derived Neurotrophic Factor (GDNF) in the striatum	Repeated ketamine administration elicits histone deacetylation and DNA methylation, effects opposite to those elicited by clinically relevant doses	[235]
STUDIES ON THE DELETERIOUS EPIGENETIC EFFECTS OF KETAMINE IN VITRO		
Main findings	**Significance**	**Ref.**
Ketamine dose-dependently inhibits the expression of HDAC6 and its nuclear import. Ketamine decreases dendritic growth, dendrite branches, and dendritic spine density in medium spiny neurons in a time- and concentration-dependent manner	Ketamine elicits neurotoxic effects in in vitro GABAergic neurons through HDAC6 inhibition	[248]
In PC12 neuronal cells, ketamine dose-dependently decreases the expression of the neuroprotective miR-429. This effect is accompanied by an increase in caspase 3 and reactive oxygen species (ROS) activity, and a dose-dependent increase in the miR-429 target BAG Cochaperone 5 (BAG5), expression. miR-429 overexpression is sufficient to attenuate the neurotoxic action	Ketamine elicits a dose-dependent neurotoxic effect in the PC12 neuronal cell line, mediated by its inhibitory effects on miR-429. Specific miRNAs are responsible for the in vitro neurotoxic effects of ketamine	[210]
Ketamine downregulates miR-22 in PC12 cells and upregulates BAG Cochaperone 5 (BAG5) in a dose-dependent manner. Lipoxin A4 methyl ester decreases these effects, attenuating neurotoxicity	Ketamine elicits a dose-dependent neurotoxic effect in PC12 cells, mediated by its effects on the miR-22/BAG5	[249]
Ketamine at higher doses increases miR-375 expression and decreases cell viability, neurite outgrowth, and BDNF levels, while increasing ROS production in human embryonic stem cell-derived neurons. miR-375 inhibition ameliorates these effects	Ketamine elicits dose-dependent neurotoxic effects in human embryonic stem cell-derived neurons, mediated partly by its inhibitory effects on miR-375. Specific miRNAs are involved in the in vitro neurotoxic effects of ketamine at higher doses	[215]
Ketamine exposure in CA1 hippocampal cell cultures increases miR-124 expression. miR-124 inhibition partially decreases the ketamine-induced neurotoxicity and upregulates the expression of AMPA, phospho-Glutamate Ionotropic Receptor AMPA Type Subunit 1 (GluR1), p-PKC, and p-ERK. Repeated high-dose ketamine in young mice leads to memory impairments during adulthood, and these effects are partially normalized by miR-124 antagonism	The neurotoxic effects elicited by higher dose ketamine in hippocampal cell culture and young mice might be mediated by miR-124 upregulation, which results in decreased AMPA, p-GluR1, p-PKC, and p-ERK hippocampal levels	[237]
Ketamine elicits a dose-dependent miR-107 (an upstream regulator of BDNF). Ketamine induces apoptosis and neurite degeneration in embryonic stem cells-derived neurons. miR-107 downregulation attenuates these effects	Ketamine elicits neurotoxic effects in embryonic stem cells-derived neurons at least partially through miR-107 signaling	[247]
Ketamine decreases the expression of the lncRNA Long Intergenic Non-Protein Coding RNA 641 (LINC00641), leading to increased neuronal apoptosis. Downregulation of LINC00641 results in an increase in its target miR-497-5p and a decrease in BDNF expression, which is repressed by miR-497-5p inhibition. LINC00641 improves ketamine-induced neuronal injury by activating the TRKB/Phosphoinositide 3-kinases (PI3K)/Protein Kinase B (Akt) signaling pathway	The neurotoxic effects of high-dose ketamine in vitro might be mediated by LINC00641/miR-497-5p/BDNF signaling	[214]
Ketamine elicits lncRNA SPRY4 Intronic Transcript 1 (SPRY4-IT1) upregulation, dose-dependent apoptosis, and neurite degeneration in human embryonic stem cells-induced neurons. Lentivirus-mediated SPRY4-IT1 downregulation protects against ketamine neurotoxicity. Enhancer Of Zeste 2 Polycomb Repressive Complex 2 Subunit (EZH2) expression is positively correlated with SPRY4-IT1 in hESC-induced neurons. EZH2 overexpression markedly reverses the protective effects of SPRY4-IT1 knockdown on ketamine neurotoxicity	The lncRNA SPRY4-IT1 is involved in the neurotoxicity elicited by ketamine in human embryonic stem cell-derived neurons, possibly through the regulation on EZH2 gene	[250]

Table 1. continued

STUDIES ON THE DELETERIOUS EPIGENETIC EFFECTS OF KETAMINE IN VITRO		
Main findings	**Significance**	**Ref.**
Repeated ketamine upregulates miR-206 expression. Repeated ketamine downregulates KCNQ1 Opposite Strand/Antisense Transcript 1 (KCNQ1OT1) and BDNF expression. Repeated ketamine induces hippocampal apoptosis in rats, and the apoptosis of PC-12 cells	The KCNQ1OT1/miR-206/BDNF axis may represent a regulatory mechanism mediating ketamine-induced neural injury	[243]
Ketamine increases the expression of the BDNF antisense RNA (BDNF-AS) and decreases that of BDNF in mouse embryonic neural stem cells-derived neurons, leading to apoptosis. BDNF-AS downregulation activates Neurotrophic Receptor Tyrosine Kinase 2 (TRKB) signaling, protects against the ketamine-induced apoptosis and promotes neurite outgrowth	The neurotoxic effects of ketamine in vitro might be mediated by a modulation of BDNF-AS	[251]
Repeated high-dose ketamine upregulates hippocampal miR-34a, which targets the Fibroblast Growth Factor Receptor 1 (FGR1) gene, and elicits apoptosis in hippocampal CA1 neurons. Inhibition of miR-34 decreases these effects	Repeated high-dose ketamine elicits hippocampal damage at least partially through miR-34a-FGR1 signaling	[241]
Ketamine downregulates the lncRNA Small Nucleolar RNA Host Gene 16 (SNHG16), and it induces apoptosis and oxidative stress in human embryonic stem cell-derived neurons. SNHG16 overexpression attenuates the ketamine-induced neurotoxicity. Neuronal Differentiation 1 (NeuroD1) gene inhibition reverses the protective effect of SNHG16 on ketamine-induced neurotoxicity	Ketamine elicits neuronal damage at least partially through downregulation of the lncRNA SNHG16	[246]
STUDIES ON THE EPIGENETIC EFFECTS OF LSD IN ANIMALS		
Main findings	**Significance**	**Ref.**
Repeated LSD modulated DNA methylation in 635 CpG sites of the mouse PFC, and the expression level of 181 proteins. Gene signaling pathways affected are involved in nervous system development, axon guidance, synaptic plasticity, quantity and cell viability of neurons, and protein translation	LSD affects the DNA methylation, and gene and protein expression related to neurotropic-, neurotrophic- and neuroplasticity signaling	[69]
Acute LSD increases histone acetylation in the midbrain and cortex, but not cerebellum of rabbits. RNA production is also increased	Acute LSD induces histone acetylation in the cortex and midbrain, which increases gene expression	[98]
LSD decreases the interaction between nucleic acids and proteins	LSD might directly bind DNA or histone proteins, affecting chromatin structure	[268]
d-LSD binds to helical DNA (less so to denaturated DNA or RNA) with max 1 molecule per base moiety	LSD might directly bind chromatin, altering its structure, and affecting its functioning	[199]
LSD causes structural changes to the DNA double-helix conformation, possibly through intercalating DNA	LSD might cause the dissociation of DNA from histones through neutralizing the phosphate anions on the DNA double-helix backbone	[197]
LSD and tryptamines bind to DNA	LSD and tryptamines might directly interact with chromatin, affecting gene expression	[198]
A racemic mixture of l-LSD and d-LSD leads to LSD-DNA Binding. l-LSD but not d-LSD may bind to DNA directly	LSD might directly bind DNA	[197]
STUDIES ON THE EPIGENETIC EFFECTS OF MDMA IN HUMANS		
Main findings	**Significance**	**Ref.**
The increase in methylation level of one CpG site (cg08276280) in the corticotropin-releasing factor receptor 1 gene and one (cg01391283) within the glucocorticoid receptor gene in saliva samples correlates with symptom reduction in individuals with severe PTSD receiving MDMA-assisted psychotherapy	A modulation of DNA methylation in stress-responsive genomic regions might be involved in the therapeutic effects of MDMA-assisted psychotherapy in individuals with severe PTSD	[83]
STUDIES ON THE DELETERIOUS EPIGENETIC EFFECTS OF MDMA IN ANIMALS		
Main findings	**Significance**	**Ref.**
Acute MDMA increases me3H3K4 (*permissive*) at the promoters of nociceptin/orphaninFQ (pN/OFQ)-NOP and dynorphin (DYN)-KOP DNA regions. Acute MDMA increases acH3K9 (*permissive*) and decreases me2H3K9 (*repressive*) at the pDYN (coupled to transcriptional upregulation). Acute and repeated MDMA decrease acH3K9 (*permissive*) at the pN/OFQ promoter (coupled to transcriptional downregulation)	Acute and repeated MDMA administration upregulates the DYN system and downregulates the N/OFQ system via modulating histone PTMs in promoter DNA regions in the nucleus accumbens	[232]
Chronic MDMA leads to cardiac gene promoters hypermethylation and circadian-related gene expression changes, coupled to cardiac hypertrophy and progressive damage	MDMA abuse affects cardiac DNA methylation, and this might be involved in cardiotoxicity	[217]

Table 1. continued

STUDIES ON THE EPIGENETIC EFFECTS OF AYAHUASCA IN HUMANS		
Main findings	**Significance**	**Ref.**
STUDIES ON THE EPIGENETIC EFFECTS OF AYAHUASCA IN HUMANS		
Main findings	Significance	Ref.
Repeated Ayahuasca in ceremonial settings affects the methylation level of 5 CpG sites located in the BDNF promoter (more so in individuals with greater childhood trauma) but does not affect the methylation level of one CpG site within the FKBP Prolyl Isomerase 5 (FKBP5) gene. These effects are accompanied by decreases in anxiety and depression detectable for up to 6 months	Repeated Ayahuasca administration in ceremonial settings elicits sustained antidepressant and anxiolytic effects which are accompanied by DNA methylation changes in the regulatory region of the BDNF gene	[79]
Hypothesis- Ayahuasca might contribute to fear extinction learning and memory reconsolidation via a Sigma-1 receptor-mediated epigenetic mechanism	Ayahuasca might modulate epigenetics processes, and these effects might be involved in the therapeutic effects of Ayahuasca over traumatic memories, fear extinction, and memory reconsolidation	[80]
STUDIES ON THE EPIGENETIC EFFECTS OF 2,5-DIMETHOXY-4-IODOAMPHETAMINE (DOI) IN ANIMALS		
Main findings	**Significance**	**Ref.**
DOI affects the acetylation level of the transcriptional enhancer histone H3K27 in neuronal cells of the mouse PFC with highly specific spatio-temporal dynamics and for up to 7 days post-administration. These changes result in transcriptomics shifts, and a structural (5-HT_{2A}-mediated) and functional modulation of synaptic plasticity, and decreased depressive-like behavior	A single DOI administration elicits long-lasting acetylation and transcriptional changes which are accompanied by long-lasting structural and functional modulation of synaptic plasticity	[107]
STUDIES ON THE EPIGENETIC EFFECTS OF B-CARBOLINES		
Main findings	**Significance**	**Ref.**
β-carbolines directly interact with DNA in vitro with affinity harmine>harmalol>harmaline>tryptoline	β-carbolines might affect chromatin compaction via direct interaction or via interacting with chromatin-remodeling complexes	[196]
STUDIES ON THE EPIGENETIC EFFECTS OF PSILOCYBIN		
Main findings	**Significance**	**Ref.**
Psilocybin at the dose of 10 mg/kg increases oxidative DNA damage in the PFC and hippocampus	Higher-than clinically-relevant doses of psilocybin elicit DNA damage in the PFC	[260]
Hypothesis- Psilocybin might affect genetic aging via epigenetic regulation of telomere length	Psilocybin might affect epigenetics processes involved with aging, preventing telomere degradation	[68]

and in vitro, while increasing BDNF and decreasing apoptosis [147–149]. Ketamine time-dependently modulated the transcription of a cluster of hippocampal (but not PFC) miRNAs (764-5p, 1912-3p, 1264-3p, 1298-5p, and 448-3p) which are hosted in the 5-HT_{2C} gene locus, mediated by the inhibition of glycogen synthase kinase 3 [150]. Acutely, ketamine increased the prefrontal level of miR-148a-3p and decreased miR-128-3p, miRNAs involved with the ubiquitin proteasome system [151]. Ketamine also elicited immunomodulatory prophylactic effects in lipopolysaccharide (LPS)-treated mice through miR-149 [152], indicating that some of the immunomodulatory effects of ketamine involved in its antidepressant effects [153] might be mediated by ncRNAs.

Similarly to what observed with conventional antidepressants [140, 154–159] the miRNome might predict the therapeutic response elicited by RAADs. For example, the non-responder status to ketamine was predicted by lower pretreatment level of miR-548d-5p and miR-605 in individuals with neuropathic pain [160, 161]. However, in a study in individuals with treatment-resistant depression receiving a ketamine infusion, no significant effects on whole blood miRNA levels were detected 24 hours after [162]. Further studies are required to identify miRNAs that can predict favorable treatment outcome in response to RAADs to increase therapeutic precision.

Circular RNAs (circRNAs), ncRNAs generated by back-splicing, have extensive complementarity to target mRNAs and can encode proteins or increase the expression of the target gene(s) [163]. A regimen of repeated ketamine in rats increased the hippocampal expression of 4, and decreased the expression of 1 circRNA, with predicted downstream effects on genes involved in calcium signaling, G protein signaling, protein phosphorylation, Mammalian Target of Rapamycin (mTOR) signaling, transcription, alternative splicing, and neuroplasticity [164]. Long non-coding RNAs (lncRNAs) are a class of ncRNAs longer than 200 nucleotides with brain area-specific expression patterns involved with neural differentiation and plasticity [165]. lncRNA dynamics are stress- and antidepressant-responsive, are altered in several neuropsychiatric disorders including Major Depressive Disorder (MDD), and might predict the antidepressant response [118, 127, 166]. For example, greater decreases of the lncRNA FEDORA predicted the decrease in depression severity following ketamine in individuals identifying as female who experience MDD [167].

POTENTIAL MECHANISMS OF RAPID-ACTING ANTIDEPRESSANTS-INDUCED EPIGENETIC CHANGES

Neuronal activity-mediated epigenetic effects

One mechanism through which psychedelics might affect the epigenetic regulation of neurotrophic-related gene expression is via neuronal activity-induced modification of chromatin structure and accessibility. The membrane depolarization of cortical neurons results in chromatin remodeling and enhanced BDNF gene accessibility via a) decreased methylation of BDNF promoter III and IV [168, 169], b) H3K4 dimethylation of BDNF promoter IV, and c) HDAC1 and mammalian Switch-independent 3 A promoter

dissociation [169]. Additionally, upon neuronal depolarization, CaMKII-mediated phosphorylation and release of the methyl-binding protein MeCP2 from the BDNF promoter III permits BDNF promoter III-dependent transcription, causing dendritic plasticity in neurons [168, 170]. Additionally, the ketamine-induced loss of somatostatin-expressing interneurons dendritic inhibition leads to heightened synaptic calcium transients in the dendritic spines of pyramidal neurons in the PFC. This process might play a role in the epigenetic effects observed following ketamine administration through altered calcium signaling, leading to increased activity-dependent synaptic plasticity [171–173]. DOI activates specific subsets of 5-HT_{2A}- and metabotropic glutamate receptor 2 (mGlu2)-expressing glutamatergic neurons and interneurons, as well as astrocytes of deep-layer prefrontal and somatosensory cortices, the claustrum, and the insula [174], and this activation might be involved in the sustained epigenetic and antidepressant-like effects elicited [107]. A single administration of DOI induced prolonged alterations in the acetylation level of neuronal transcriptional enhancers, causing sustained effects over axonogenesis, synapse organization, assembly, and function, and receptor internalization and activity [107]. Despite this preliminary correlative evidence, given that physiological neuronal activation itself can profoundly modulate the epigenetic landscape de novo [175], this calls into questions whether the epigenetic effects elicited by RAADs are causally involved in the therapeutic effects, or neuronal activity-driven changes. Future studies are encouraged to address this research question.

5-HT receptors signaling-mediated epigenetic effects

Psychedelics might activate similar epigenetic mechanisms to those activated by endogenous 5-HT signaling through various 5-HT receptors. 5-HT triggers a transient remodeling of chromatin structure mediated by 5-HT_{1A} and BDNF-TRKB signaling which decreases HDAC5 expression, and increases cortical H3K9 acetylation of the BDNF promoter and BDNF levels, reinstating plasticity in the adult nervous system [176]. 5-HT signaling also induces changes in the methylation status of the promoter of CREB2, a plasticity-related transcription factor involved in long-term facilitation [177, 178]. The properties of psychedelics resemble those of 5-HT: they interact with 5-HT receptors such as the 5-HT_{1A} and 5-HT_{2A} receptors, triggering biased signaling and the transcription of genes involved in neurotransmission, neuroplasticity, and neuroimmunomodulation [14–16]. Given that these 5-HT receptors are fundamentally involved in governing cortical circuits mediating cognitive and executive functions [179, 180], the activation of these receptors by RAADs might result in specific epigenomic fingerprints and chromatin architecture changes, ultimately leading to structural and functional synaptic changes. The epigenetic effects elicited in discrete cell types through activation of 5-HT receptors, might alter circuit and network activities, putatively mediating therapeutic improvement at the circuit-, network-, and system-levels.

TRKB signaling-mediated epigenetic effects

Like classical antidepressants [181], a mechanism that might mediate the epigenetic effects of RAADs is the activation of endogenous BDNF signaling through direct binding to and activation of the TRKB receptor [182–185]. Activation of TRKB signaling results in the activation of other cascades such as the CaMKII, RAS/MAPK and phosphoinositide 3 kinase pathways [14, 17, 186–188]. Moreover, TRKB signaling leads to altered chromatin structure of the BDNF gene, and transcriptional upregulation of the BDNF gene and its downstream effector target AKT Serine/Threonine Kinase 1 (Akt)-mTOR. These events ultimately cause an increase in neuroplasticity, synaptic potentiation, and antidepressant effects. The outcome is the reopening of a period of structural and functional plasticity within the CNS that can be harnessed therapeutically [182–184, 189, 190]. Supporting a fundamental role of the reopening of critical periods of plasticity, RAADs lead to the degradation of the extracellular matrix in the NAc, creating the prerequisites to enable metaplasticity [190]. Whether epigenetic mechanisms are involved in this process remains unknown.

Interestingly, the epigenetic changes elicited by LSD resemble those observed during critical periods of neurodevelopment and synaptic plasticity, thus seemingly re-creating in the adult nervous system the epigenetic correlates observed during neurodevelopment and learning [69]. Indeed, CCAAT enhancer binding protein beta (CEBP2), a co-activator and target gene of CREB, was a "top-hit" in the PFC in terms of differential DNA methylation following repeated LSD [69]. In accordance, CEBP2 together with several other neuroplasticity-related genes is dose-dependently transcriptionally modulated in the PFC following psilocybin administration [191]. Accordingly, a single administration of psilocybin following chronic stress during adolescence in rats was sufficient to normalize depressive-like and cognitive-like behaviors [192]. Lastly, given that (i) psychedelics interact with TRKB, 5-HT_{2A}, and mGlu2 receptors, that (ii) TRKB interacts with the 5-HT_{2A} [193] and the mGlu2 [194] receptors, and that (iii) the latter two receptors interact with each other [195], these interactions may be functionally relevant from an epigenetic standpoint.

Direct interaction with DNA, histones, or chromatin remodeling complexes

Another intriguing mechanism supported by several lines of evidence is that RAADs may directly interact with DNA, histones, or chromatin remodeling complexes, thus acting as direct epigenetic modulators. Indeed, the β-carbolines contained in the brew Ayahuasca directly interact with DNA in vitro [196], and early studies observed that LSD directly binds DNA or histone proteins [197–199]. For psychedelics to interact with DNA or histones in vivo, they would first need to reach the intracellular space and the nucleus. Indeed, membrane permeability is essential for the neuroplastic effects of psychedelics, and ligand-bound 5-HT_{2A} receptors are internalized in vivo and in vitro [200–203]. Additionally, neurotrophic factors are uptaken and transported to the cell body through retrograde axonal transport. Given that RAADs bind the TRKB receptor [186], they might similarly be internalized by nerve terminals. In support of this hypothesis, DMT is internalized via a three-step process requiring active transport: 1) it is actively transported across the blood-brain barrier, 2) acts as a 5-HT transporter substrate on the neuronal plasma membrane, and 3) it is internalized by neuronal cells, and stored into synaptic vesicles by the neuronal vesicle monoamine transporter 2 for up to 1 week [204–206]. Whether the sequestered DMT in synaptic vesicles or the DMT-activated Sigma-1 receptor interact with DNA or chromatin remodeling complexes remains to be assessed [206, 207]. Recently, it was reported that 5-HT can covalently bind to glutamine 5 on the trimethylated H3K4 histone, eliciting a permissive transcriptional influence that modulates the interaction of histone PTMs with chromatin readers during neuronal differentiation [109]. Due to the structural similarity of 5-HTergic psychedelics to 5-HT, it remains to be assessed whether they modulate the relationship between histone PTMs and chromatin readers.

The mechanisms discussed here are not necessarily mutually exclusive and may be part of a series of events responsible for reopening a period of neurodevelopmental-like neuroplasticity, providing a neurobiological substrate that can be harnessed therapeutically. Achieving this seems to require appropriate support and integration before, during, and following psychedelic-assisted psychotherapy. Given that the different mechanisms modulating chromatin structure and DNA accessibility may interact with one another, deciphering the "psychedelic epigenome" represents a new frontier in psychiatry.

INVOLVEMENT OF EPIGENETIC MECHANISMS IN THE POTENTIAL SIDE EFFECTS ELICITED BY RAADS

While preliminary evidence suggests that the epigenetic effects induced by RAADs may contribute to therapeutic improvement, uncertainties persist regarding side effects. Studies have documented epigenetic alterations following the abuse of RAADs, which appear antithetical to those elicited by clinically relevant doses, yet similar to those elicited by stress. These changes are reminiscent of neuronal, immune and cardiac dysfunction. Most of the potential epigenetic-mediated side effects associated with RAADs were observed following repeated administration of higher doses of ketamine during gestation, lactation, and the neonatal period (Table 1).

Immune-related side effects

High or repeated doses of ketamine may cause side effects through the epigenetic modulation of immune function, via (i) upregulation of permissive H3K4 trimethylation, (ii) downregulation of repressive H3K27 and H3K36 trimethylation, and (iii) DNA hypomethylation at nuclear factor-κB (NF-κB)-responsive promoters [208, 209], as well as iv) modulation of proinflammatory, neurotoxic, and oxidative signaling through RNA regulatory pathways [152, 210–216]. Repeated MDMA administration also causes epigenetic marks reminiscent of immune dysfunction such as hypermethylation of the Terminal Nucleotidyltransferase 5B gene, a chaperone involved with cyclooxygenase 2 maturation [217]. Future studies are warranted to further investigate potential epigenetics-mediated immune side effects arising from repeated use and abuse of RAADs.

Cardiac hypertrophy

In a model of ketamine abuse during early gestation, ketamine decreased the acetylation level of cardiac histone H3K9 at the Myosin Light Chain 2 promoter by increasing HDAC3 level and histone deacetylase activity. These effects were accompanied by altered expression of several genes related to cardiomyogenesis, resulting in enlarged heart and ventricular chamber, thinner ventricular wall, degeneration of cardiomyocytes, and reduced systolic function [218]. Repeated MDMA exposure also led to hypermethylation of cardiac DNA promoter regions resulting in cardiac hypertrophy and progressive damage [217]. Given the concern surrounding the potential impact of RAADs on cardiovascular function through cardiac 5-HT receptors [219], future investigations are recommended to explore potential deleterious effects at clinically relevant doses and regimens.

Deleterious gestational and transgenerational effects

While few studies have assessed the transgenerational effects of RAADs, maternal intake during pregnancy and lactation may similarly to conventional antidepressants lead to epigenetic modifications and altered anxiety and depressive-like behavior in the offspring [56, 220–222]. For example, ketamine abuse during gestation impacts the epigenetic make-up of the fetus, and can result in impaired neurocognitive function in the offspring [218, 223]. Similarly, sociability, emotional behavior, and increased PFC dopamine levels are observed in the offspring of rats following repeated Ayahuasca administration during pregnancy and lactation [224].

Potential for addiction

While there is general consensus that psychedelics have low potential for addiction, psychological dependence or reinforcing effects, the NMDA antagonist ketamine [225, 226] and the empathogen MDMA [227, 228] have been associated with drug-seeking behaviors accompanied by epigenetic changes, similarly to drugs of abuse [229, 230]. For instance, one study found that ketamine-induced conditioned place preference resulted in differential expression of 34 hippocampal miRNAs [225], while another study showed that the conditioned place preference was accompanied by altered expression of serum exosomal miRNAs associated with processes such as nervous system development, neuron generation and differentiation, and apoptosis [231]. Acute and repeated MDMA exposure altered histone PTMs in the NAc promoter regions of the opioid-related nociceptin/orphaninFQ (N/OFQ)- Nociceptin Receptor (NOP) and dynorphin (DYN)- Kappa-Opioid Receptor (KOP) systems [232]. Specifically, acute MDMA increased the H3K4 methylation at N/OFQ and DYN promoters, while increasing H3K9 acetylation and decreasing H3K9 dymethylation at the DYN promoter. Acute and repeated MDMA also decreased H3K9 acetylation at the N/OFQ promoter [232]. These opioidergic effects could have direct implications for the therapeutic effects of MDMA on trauma [233], and for MDMA's potential for addiction and neurotoxicity [234]. Considering the known involvement of epigenetics and transcriptional changes in addiction, it is prudent to investigate through cell-type and brain area-specific approaches whether epigenetic mechanisms may play a role in putative addictive, or anti-addictive, properties of RAADs.

Neurotoxicity

Several studies have reported neurotoxic effects of RAADs arising from repeated administration or higher doses. While such effects are not triggered in vivo by clinically relevant doses, this knowledge remains relevant from a harm-reduction perspective. Repeated ketamine increased histone deacetylase and DNMT activity, in an opposite fashion to the homolog changes elicited by clinically-relevant doses [235]. Additionally, repeated high-dose ketamine in young mice led to neurotoxicity, neuronal degeneration and memory impairments during adulthood, at least partially through miR-34c [236], miR-124 [237], miR-137 [238], and miR-199a-5p [239] signaling. In adolescent rats, repeated ketamine high-doses elicited hippocampal apoptosis and cognitive impairments, putatively mediated by hippocampal miR-214 downregulation/ Phosphatase And Tensin Homolog upregulation [240] and miR-34a upregulation/ Fibroblast Growth Factor Receptor 1 downregulation [241]. Repeated high-dose ketamine also elicited schizophrenia-like behavior accompanied by modulation of the miRNome and neurotrophic-related gene expression in the PFC and hippocampus [242, 243]. In vitro studies corroborate the neurotoxic effects of ketamine at higher doses through epigenetic mechanisms involving HDAC6, miR-22, miR-124, miR-497-5p, the lncRNAs SPRY4-IT1, LINC00641, and SNHG16, and the BDNF antisense RNA [214, 215, 237, 244–251]. Together, future research exploring the neurotoxic effects of RAADs abuse through epigenetic changes is encouraged.

Cancer

Several of the epigenetic effects elicited by RAADs involve signaling cascades related to cell growth, proliferation, and cancer, such as mTOR and BDNF [252, 253]. Therefore, epigenetic changes in these genes might induce or affect the progression of cancer. Considering that psychedelic-assisted psychotherapy is a promising treatment to attenuate psychological and existential distress in individuals facing a life-threatening conditions such as cancer, it is important to assess the neoplastic potential of RAADs [254–256]. If RAADs affected DNA methylation and other epigenetic mechanisms indiscriminately, for example by increasing or decreasing global DNA methylation aspecifically, this could pose a risk factor by causing genomic instability or repressing the transcription of tumor-suppressor genes [257–259]. A recent study reported oxidative DNA damage following the administration of higher-than clinically-relevant doses of psilocybin in the PFC and hippocampus [260]. Early reports suggested that ingesting or being exposed *in utero* to psychedelics such as LSD might be mutagenic and cause chromosomal damage and potential delayed mutations in the offspring (reviewed in [261]). However,

subsequent experimental and epidemiological studies failed to replicate the findings, even in long-term psychedelic users [261, 262]. One investigation found that ketamine elicited ferropoptosis, and may thus elicit anti-neoplastic effects through the lncRNA Pvt1 oncogene /miR-214-3p signaling [263]. Given this evidence, further studies are warranted to investigate the potential of RAADs to induce, accelerate, or perhaps counteract, cancer.

CONCLUSION

Preliminary correlative evidence indicates that the epigenetic mechanisms engaged by RAADs converge, like conventional antidepressants, on permissive mechanisms over chromatin areas involved in neuroplasticity within stress-vulnerable brain regions. Importantly, these epigenetic changes counteract those induced by psychosocial stress, early-life adversities, and substance abuse. Yet, the abuse of RAADs triggers epigenetic marks resembling those elicited by stress.

Significant knowledge gaps remain, such as the mechanistic relationship between RAADs and epigenetic effects, the timing of onset of these epigenetic changes and their duration, the mechanisms responsible, cell type specificity, the role of metabolites, and the effects of "microdosing" (the ingestion of $1/10^{th}$–$1/20^{th}$ of a "large" dose). The polypharmacological nature of RAADs implies that each compound, dose, and regimen may uniquely affect the epigenetic control of gene expression, with potential indications or contraindications for various psychiatric disorders. Understanding how the subjective experience and environment modulate the epigenetic effects accompanying the administration of RAADs is an area ripe for exploration. Determining the potential modulation by the environment on the epigenetic effects of psychedelics could inform ongoing clinical investigations and expand our understanding of epigenetics. Brain area- and cell type-specific methods, facilitated by techniques like cell-sorting approaches and single-cell *omics* approaches, could address these questions [264, 265]. Identifying predictors [266] and modulators (i.e., set and setting, placebo effect) [267] of epigenetic responses accompanying RAADs administration could lead to improved therapeutic precision and efficacy.

While the epigenetic outcomes may causally contribute to therapeutic benefits, causative investigations lack. Given that epigenetic changes are observed in all cell types under disparate conditions (for example following neuronal activity or neurotoxic stimuli), the observed epigenetic changes could be secondary to behavioral changes induced by psychedelics. The potential epigenetic-mediated side effects, such as immune-related effects, cardiac hypertrophy, gestational and transgenerational effects, and cancer, also require further investigation. Future studies addressing these knowledge gaps could lead the way for developing novel neuroepigenetics-based precision therapeutics.

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COMPETING INTERESTS

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ADDITIONAL INFORMATION

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