

# Epigenetic aspects of posttraumatic stress disorder

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**Abstract.** Development of psychiatric diseases such as posttraumatic stress disorder (PTSD) invokes, as with most complex diseases, both genetic and environmental factors. The era of genome-wide high throughput technologies has sparked the initiation of genotype screenings in large cohorts of diseased and control individuals, but had limited success in identification of disease causing genetic variants. It has become evident that these efforts at the genomic level need to be complemented with endeavours in elucidating the proteome, transcriptome and epigenetic profiles. Epigenetics is attractive in particular because there is accumulating evidence that the lasting impact of adverse life events is reflected in certain covalent modifications of the chromatin.

In this review, we outline the characteristics of PTSD as a stress-related disease and survey recent developments revealing epigenetic aspects of stress-related disorders in general. There is also increasing direct evidence for gene programming and epigenetic components in PTSD. Finally, we discuss treatment options in the light of recent discoveries of epigenetic mechanisms of psychotropic drugs.

## 1. Introduction

The term epigenome refers to the entirety of all molecular control elements programming the genome respectively regulating gene activities. Like any molecular action, also epigenetic programming can go wrong. Accordingly, distinct epigenetic defects are reported for a variety of diseases and some of them are already known to constitute a main pathogenetic mechanism, e.g. in patients suffering from Rett syndrome.

One of the major environmental factors established as inducer of epigenetic changes is stress. Stress is known to contribute to the pathogenesis of a variety of disorders, including the majority of psychiatric disorders like major depression and posttraumatic stress disorder (PTSD). There is robust evidence for epigenetic contribution to the development of PTSD-like symptoms in rodents while so far there are only few studies demonstrating the connection between trauma-induced epigenetic changes and the onset and perpetuation of PTSD symptoms in humans. Generally, it is unlikely

that psychiatric disorders can be traced back to one single epigenetic modification, inasmuch as many different genetic variants are conveying disease susceptibility. These diseases present with highly variable clinical signs and symptoms but these diverse features cannot be linked to specific genetic and epigenetic variations. In fact it is likely that they derive from a complex web of connected but different causes.

Only a small proportion of individuals develops post-traumatic PTSD after having been exposed to a traumatic event [13]. PTSD only occurs if a (yet still unknown) biological predisposition coincides with a traumatic stressor. This instantly forces the supposition that the epigenome, especially in regard to its capacity to mediate communication between environment and genome, might grossly contribute to PTSD pathogenesis.

In this review the most important molecular epigenetic programming mechanisms are illustrated to allow for a better understanding of the following paragraphs where the dynamic principle of the epigenome including its reactivity to environmental factors and finally the current state of knowledge regarding epigenetic modifications in stress-related diseases, in particular

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PTSD-animal models and PTSD patients, are discussed on the basis of the most recent publications.

## 2. PTSD as stress-related disease

The term stress was first employed in a biological context by the endocrinologist Hans Selye in the 1930s. He later broadened and popularized his concept to include inappropriate physiological response to any demand. In his usage “stress” refers to the condition and “stressor” to the stimulus triggering the unphysiological response. It covers a wide range of phenomena, from mild irritation to drastic dysfunction that may cause severe health breakdown mostly occurring in response to maximal stressors.

These maximal stressors are also termed traumata; the term *trauma* derives from the greek word *τραυμα* meaning wound. A traumatic event involves a single, enduring or repeating experience that seriously threatens the physical or psychic integrity of the concerned person. According to DSM-IV also witnessing a serious threat or the death of another person can be classified as a traumatic event, but in any case a horrible experience can be categorized as a traumatic incident only if the individuals exposed in the course of the event experienced feelings of helplessness and massive horror. The disability to cope or integrate the ideas and emotions involved with that experience leads to the sense of being overwhelmed.

Symptoms usually arise weeks or months, in rare cases even decades after traumatic experiences. Moreover, diagnosing PTSD includes the assumption that without a traumatic event this psychiatric disease would not have been appeared. Thus, the stressor precipitated the onset of PTSD which is characterized mainly by recurrent and intrusive distressing recollections of the event (e.g. flashbacks), nervous hyperarousal and trauma-stimuli associated avoidance anxiety each lasting more than one month, thus causing significant impairment in social, occupational, or other important areas of functioning.

Like other stress-related psychiatric diseases PTSD comes along with a variety of neuroendocrinological alterations. The hypothalamus-pituitary-adrenal (HPA) axis has been the main focus of neuroendocrine research in PTSD [104].

Perception of stress leads to synthesis and release of corticotropin-releasing hormone (CRH) and vasopressin by hypothalamic nuclei which stimulate the secretion of adrenocorticotropin (ACTH) at the pituitary

which in turn elicits the release of glucocorticoids from the adrenal cortex. Then, cortisol as the final peripheral molecule exerts its actions on metabolism, immunity and brain functions. Increased and prolonged production of CRH and cortisol explain many of the behavioral, circulatory, metabolic and immune manifestations of syndromes associated with acute and especially with chronic stress, such as PTSD.

Transient HPA-system shifts were found in a variety of psychiatric diseases, e.g. it is an established finding that many patients suffering from major depression (MD) display a hyperactivity of their stress hormone system [40]. In contrast to patients with MD, many authors found an HPA-axis *hypo*activity in PTSD-patients reflected for instance by lowered serum cortisol levels [11,107] and an enhanced suppression of cortisol in the DEX/CRH-test [101,107]. However, a recent meta-analysis of 37 studies [57] found no differences in plasma cortisol levels between adult individuals with PTSD and controls. But interestingly, sub-group analyses revealed some remarkable results: both the patient cluster having experienced physical or sexual abuse and the female patient cluster exhibited significantly lower cortisol levels in comparison to their respective control subgroups. Despite the limitation of differences in data collection and assessment, that meta-analysis clearly reveals the complexity and heterogeneity of the neuroendocrine concomitants of PTSD [71].

Besides the HPA-axis, also the sympathetic nervous system (SNS) is a key circuit in PTSD pathophysiology. Its major neurotransmitter norepinephrine (NE) is an important player in the central as well as in the autonomic stress response. NE is produced in neurons of the locus coeruleus and interacts in concert with CRH and vasopressin to increase fear conditioning and memory encoding. In the periphery, stress leads to release of NE and epinephrine from the adrenal medulla, resulting in an organismic alarm reaction. Thus, NE is involved in the development of two main clusters of PTSD symptoms, namely re-experiencing symptoms and hyperarousal which is expressed inter alia with an exaggerated startle response and increased heart rate [85]. Hence it is not surprising that the most consistent findings in PTSD neuroendocrine studies are increased central and peripheral noradrenergic activities [32,104].

Taken together, PTSD is a stress-related disease not only because PTSD symptoms are precipitated by a traumatic stressor but also because this severe psychiatric condition is accompanied by drastic alterations in the two major stress hormone systems.

### 3. The epigenome

The term epigenetics has been coined even long before the structure of genes has been discovered [36, 95]. In today's biomedical research, epigenetics explores the regulatory functions of covalent chromatin modifications as well as of microRNAs in gene activity. These chromatin modifications do not alter the genetic information *per se*, but govern access to it and can be maintained and stably inherited through mitosis and meiosis. The modifications comprise in mammals predominantly the post-replicative attachment of a methyl group at carbon position 5 of the nucleobase cytosine as well as acetylation, methylation and phosphorylation of histone proteins at defined amino acid positions [45]. More rare modifications are sumoylation [81], ubiquitination [82], ADP-ribosylation [37], biotinylation [16], carbonylation [100], deimination [23], proline isomerization [66], and glycosylation [43] of histones.

In extension of a model that was based on the link between histone acetylation and gene transcription [92], Strahl and Allis proposed a general "histone code" model for the combinatorial function of specific post-translational histone modifications in gene transcription [87]. According to this concept, the combinatorial arrangement of distinct histone modifications forms a code that is read and interpreted by nonhistone chromatin associating proteins that signal the encoded information to downstream functions such as gene transcription. Since a nucleosome comprises several histones, this combination results also in a "nucleosome code", allowing a plethora of epigenetic states.

The histone modification status, in particular histone acetylation, is intimately linked to the degree of DNA methylation [64]. DNA can be methylated in mammals at cytosines residing in CpG dinucleotides. 60–80% of these dinucleotides are methylated in humans [75]. In general, CpG dinucleotides are grossly underrepresented in the genome. This has been explained by the impossibility for the cellular repair machinery to specifically correct a deaminated methylated cytosine, which leads to the legitimate DNA nucleoside thymine, while deamination of unmethylated cytosine produces uracil, which can easily be recognised as a non-DNA nucleoside. CpGs are enriched in so called "CpG-islands" [30], which are usually found in the 5' regulatory regions of most genes. DNA methylation usually leads to gene silencing through effects on chromatin structure. This can involve more general mechanisms leading to hypoacetylation of histones and formation of condensed chromatin [8,9]. Methy-

lated DNA is recognised and bound by a family of methylated DNA binding proteins of which methyl-CpG-binding protein2 (MeCP2) has attracted particular attention. MeCP2 recruits the histone deacetylase (HDAC) complex mSin3A, thereby attracting HDAC-1 and HDAC-2, thus ultimately abolishing histone acetylation and inactivating chromatin [44]. DNA methylation can, in addition, impede DNA binding of transcription factors [89,93]. However, DNA methylation could also be associated with increased gene transcription if it interferes with DNA binding of a repressor.

A wealth of enzymes executing the addition and removal of covalent chromatin modifications has been found, albeit the exact mechanism of active cytosine demethylation has not been elucidated yet. As key executors of diverse regulatory signals these enzymes are target of intense drug development efforts.

### 4. Epigenetic aspects of stress-related psychiatric diseases

While epigenetic mechanisms have been under investigation in cancer and developmental research for decades [10], they recently attracted intensified attention by neuroscientists as a potential mediator of gene environment interactions. Environmental insults impacting on the epigenome may represent the molecular programming of stable long-term effects on gene expression in the brain, and thus on cerebral function.

Most of the experimental evidence for the role of epigenetic mechanisms in stress-related psychiatric diseases originates from animal models. Psychiatric diseases pose a particular challenge for researchers aiming at modelling diseases in animals [46,60]. Nevertheless, several models have been established, based on the realisation of stress as central risk factor for the development of psychiatric diseases. Common to the diverse animal models is the exposure of the animal to stress during a sensitive period in life, i.e. in the prenatal, postnatal and adolescent phase. This is in congruence with the observation in humans that adults who suffered from severe early life stress such as parental loss or neglect presented with higher basal levels of stress hormone and were at greater risk of developing mood disorders [65].

Already more than half a century ago, disturbances of the mother-neonate interaction in rodents have been demonstrated to alter adult phenotypes that include neuroendocrine function, behaviour, metabolism and cognition, e.g. [49]. For example, rats experiencing

maternal separation in the first weeks of life develop increased anxiety and cognitive deficits later in life [72, 73]. Programming of HPA axis (re)activity has been extensively investigated as a critical juncture between early life environment and health in the adult [24,29,67, 86]. These alterations of HPA axis settings frequently go along with changes in GR expression [28,50,96], whose activation is pivotal for balancing HPA activity through negative feed-back loops at the level of CRH, vasopressin, and ACTH [24]. Importantly, blunting the early life experience-induced differences in hippocampal GR expression blocks the effects on HPA activity in adulthood [55,56]. Moreover, loss of GR expression in the hippocampus leads to dysfunctional HPA axis regulation and enhanced anxiety-related behaviour [12], further corroborating the notion of programming hippocampal GR levels as the underlying mechanism translating early life experience into differential HPA reactivity and differences in the HPA-associated behavioural spectrum.

The early life-induced programming of GR levels has been directly linked to epigenetic alterations of the GR gene. More specifically, in animals experiencing different maternal care, disparate DNA methylation patterns and chromatin acetylation levels (acetylation at lysine 9 of histone 3) were identified in the exon 17 promoter of GR [96], which is the relevant regulatory region determining GR expression in the hippocampus [52]. The change in DNA methylation was linked to impaired binding of the transcription factor nerve growth factor-inducible protein A, whose response element harbored differentially methylated cytosines [96]. This example provides intriguing molecular insight into the epigenetic mechanisms underlying experience-induced programming of neuroendocrine circuits and behaviour.

In a more recent study, early life stress was found to cause a persistent increase of vasopressin, accompanied by sustained DNA hypomethylation of a relevant regulatory region [62]. This hypomethylation affected CpG dinucleotides that are recognised by MeCP2. Intriguingly, the ability of MeCP2 to bind to these sites is controlled by neuronal activity. Thus, in this model early life stress induces epigenetic marking of an HPA regulatory gene via neuronal activity-directed regulation of protein DNA interaction of MeCP2 as the molecular underpinnings of neuroendocrine and behavioral alterations that are frequent features in stress-related diseases. This finding is remarkable insofar as increased vasopressin secretion from the hypothalamic nuclei is known to induce anxiety in rodents and is elevated in

patients with depression. Moreover, individuals having experienced early life trauma have elevated cortisol [38] secretion following the Dex/CRH test, indirectly reflecting elevation of hypothalamic vasopressin. In fact in mice where HPA hyperactivity and depression- and anxiety-like behaviour was permanently induced by early life trauma, a vasopressin receptor antagonist modulated neuroendocrine and behavioural sequelae from stress-exposure.

Another common way to model the pathogenesis of depression-like states is chronic stress exposure of rodents [46]. Social defeat of an experimental mouse by serial confrontation with aggressive mice over 10 days induces depression-like syndromes such as anxiety-related symptoms, anhedonia and loss of interest in social interaction. The aptitude of this model for investigating depression-like states is further substantiated by the observations that antidepressants can reverse most of the stress-induced symptoms [7,91]. Brain derived neurotrophic factor (BDNF) was found to be stably downregulated after chronic social defeat along with methylation of lysine 27 of histone H3 (H3K27) [91], which constitutes a repressive epigenetic mark. Chronic treatment with antidepressants restored bdnf RNA expression together with reversal of the behavioural impairments. However, H3K27 methylation remained unchanged, which was suggested to represent a “molecular scar” that may contribute to the risk of reappearance of symptoms in depressed patients after discontinuing antidepressant treatment [76].

Even though in humans obvious limitations prevent insight to the same depth as in animal studies, significant evidence has accumulated for the importance of epigenetic mechanisms in psychiatric diseases. For example, a recent study examining post mortem brain tissue from suicide subjects with a history of early childhood neglect and/or abuse revealed a significant promoter-wide hypermethylation of rRNA genes [53].

In schizophrenia, alterations in GABAergic mRNA expression have been identified as a key feature. Expression of glutamate decarboxylate 1 (GAD1) has been found to be decreased in schizophrenia, in conjunction with a risk haplotype, along with reduced levels of (tri)methylation at lysine 4 of histone H3 (H3K4), a stimulatory epigenetic mark [42]. Moreover, the atypical antipsychotic clozapine increased H3K4 methylation at GAD1 and promoter occupancy with the respective methyltransferase [42]. In another study, DNA hypermethylation of the reelin gene promoter has been observed in post mortem brains from schizophrenic patients [1]. This could explain the significantly re-

duced expression of this important neuronal protein in schizophrenia [19,27]. Although reelin promoter hypermethylation was not found in another study [90], the role of DNA methylation at this promoter is corroborated by studies reporting its demethylation by the antipsychotic drugs clozapine and sulpiride [25].

DNA methylation changes related to schizophrenia and bipolar disorder have recently been discovered in a genome-wide methylation analysis using post-mortem brain tissue [59]. The study identified prominent loci of methylation changes that are involved in glutamatergic and GABAergic neurotransmission, brain development and other processes connected to disease. In addition, DNA methylation at the BDNF gene has been found to correlate with polymorphisms that previously had been associated with major psychosis [59]. A study examining the DNA methylation pattern at the X chromosome in peripheral cells of female monozygotic twin pairs that were either concordant or discordant for bipolar disease or schizophrenia provided further evidence for epigenetic mechanisms operating in disease etiology of bipolar disorder [77]. Moreover, another comparison of twin pairs concordant or discordant for bipolar disorder identified differentially methylated genes that could contribute to the pathophysiology of this disease [48].

MeCP2, an essential interpreter protein of the epigenetic mark DNA methylation, has been linked to a variety of mental dysfunctions and diseases. Rett syndrome is a neurodevelopmental disorder that is most frequently (95%) caused by spontaneous mutations in the MeCP2 gene located at the X-chromosome [5,74] and is the most frequent cause of mental retardation in females [35]. Moreover, mutations in MeCP2 have been associated with X-linked autism [74] and the Angelman Syndrome.

In an effort to translate the observations of early life stress-induced epigenetic programming of GR expression to the situation in humans, the neuron-specific GR promoter was examined for epigenetic differences between post-mortem hippocampi from suicide subjects with a known history of early life abuse and hippocampi from either suicide subjects without early life abuse or controls [54]. In suicide victims with early life abuse, the mRNA levels of GR were found to be downregulated concomitantly with elevated promoter methylation. Moreover, promoter constructs mimicking the observed methylation pattern exhibited reduced binding of the transcription factor nerve growth factor-inducible protein A [54]. These findings closely resemble the situation observed with reduced parental care as early life stressor in rodents [96,97].

In contrast to these findings in suicide victims, differential methylation of GR was not found in a very recent study focussing on major depression [3]. Levels of total GR were found to be unchanged in samples originating from individuals who had suffered from major depression, while the transcripts derived from different transcriptional start sites displayed some variation. GR exon 1F transcripts were downregulated in major depression, accompanied by reduced levels of the exon 1F transcription factor NGFI-A [3]. However, promoter 1F was found unmethylated throughout in major depression and controls. Therefore, changes in GR expression from promoter 1F are not due to direct epigenetic programming at this promoter, but more likely caused by diminished NGFI-A activity [3]. Assuming that the individuals tested in this study did not experience abuse, and in comparison with the observed methylation changes in abuse victims [54], this implies important differences in the pathomechanisms of major depression and abuse victims.

Finally, a pilot study aimed at evaluating the association of DNA methylation in buccal cells and risk for depression [68]. The methylation analysis focussed on the serotonin transporter gene (5HTT) in a sample drawn from a longitudinal study of adolescent health. In carriers of the 5HTTLPR short-allele depressive symptoms were more abundant among those with increased buccal 5HTT methylation [68]. Larger studies are underway in several laboratories to explore the possibility to develop peripheral epigenetic markers in depression.

## 5. Evidences for epigenetic modulation in PTSD

The animal models for psychiatric diseases as well as the human cohorts outlined above exhibit some phenotypic overlap with PTSD, and therefore, these findings also have shaped concepts for PTSD research [79, 102]. There are also examples for specific PTSD animal models. In a mouse model that uses inescapable electric foot shock to induce PTSD-like symptoms [83], maternal inexperience was identified as a risk factor for PTSD [84]. This points at the relevance of epigenetic factors in PTSD-like behavior. In another PTSD model in rats, predator scent stress was used [17], and the differences in hippocampal DNA methylation were assessed on a genome-wide scale between animals not responding and responding with PTSD-like symptoms [15]. The findings not only suggest changes in global methylation pattern involved in PTSD development, but also present the differentially methylat-

ed gene Disc Large-Associated Protein (DLG2) as a possible target in PTSD.

There is also persuasive evidence for crucial epigenetic processes in PTSD from clinical studies. In a *post mortem* study of patients that committed suicide mRNA levels of GR were found to be downregulated in those suicide victims that had been exposed to early life trauma. This was associated with elevated promoter methylation [54]. Moreover, it is known from a variety of studies that victims of early life stress or traumatic events like abuse or neglect exhibit significantly higher morbidity rates for a variety of disorders, especially for cardiovascular and affective diseases in their later adulthood [98]. A clinical study with pregnant women revealed that massive stress during pregnancy induces changes in epigenetic HPA axis programming *in utero* associated with an increased vulnerability for psychiatric disorders possibly transmissible to following generations [79]. Yehuda and colleagues studied mothers who were pregnant while they were exposed to the terror attack on September 11, 2001: Mothers suffering from PTSD as well as their babies exhibited significantly lower salivary cortisol levels in comparison to the exposed but PTSD-free control group [106]. Moreover, the observation that a cohort of individuals that all developed PTSD after having been exposed to the same terror attack exhibited markedly changed gene expression patterns that included genes involved in HPA regulation, again points to epigenetic modulation of gene activity [103]. Another clinical study examining the offspring of Holocaust victims also points to a trauma-induced, inheritable epigenetic modulation of the stress hormone system since serum cortisol levels were found to be significantly lower in healthy offspring of victims suffering from PTSD in comparison to those with PTSD-free ancestors [106].

A recent clinical study on epigenetics and the pathogenesis of PTSD applied methylation microarrays to assay CpG sites in leukocyte DNA from more than 14,000 genes among 23 PTSD-affected and 77 PTSD-unaffected individuals [108]. This association study revealed that immune system functions are significantly overrepresented among the annotations associated with genes uniquely unmethylated among PTSD patients. Epigenetic variability in immune function by PTSD was corroborated using an independent biological marker of immune response to infection, namely the typically latent herpesvirus CMV-a, whose activity was significantly higher among those with PTSD. Thus, this report suggests a biologic model of PTSD etiology in which an externally experienced traumatic event

induces downstream alterations in immune function by reducing methylation levels of immune-related genes, although – as with many association studies of that type – it remains unclear to what extent the leukocyte epigenome represents the cerebral epigenome.

Taken together, these examples from clinical and animal studies lead to the conclusion that during vulnerable ontogenetic episodes of different species a variety of stressors can induce epigenetic modifications with consecutive behavioral modifications which at least to some extent can be transmitted transgenerationally.

## 6. Perspectives

Considerable research efforts are underway worldwide to develop drugs that target the epigenome. These may also change the treatment regimes in PTSD. To better assess the usefulness of “epigenetic drugs”, a better understanding of the exact epigenetic mechanisms in PTSD is needed, and particular attention needs to be directed towards the specificity and mechanisms of drug action, and towards the time window of opportunity for treatment.

While it is still not proven yet that the observed epigenetic alterations are actually causal for the observed phenotypic alterations after stress, epigenetic actions of psycho-active drugs as well as psychoactivity of drugs impacting on the epigenome have been observed. For example, psychopharmaceuticals have also been shown to impact on DNA methylation, as demonstrated for specific promoters or for broader effects through inhibition of DNA methyltransferases (DNMTs) [25,70].

A large body of evidence points to the potential use of HDAC inhibitors in psychiatric diseases. Exposure to chronic social stress leads, after an initial decrease, to a persistent increase in acetylation of histone H3 in the nucleus accumbens and to a decreased level of HDAC2 [21]. The changes in H3 acetylation were reverted by the application of HDAC inhibitors, which also exerted robust antidepressant-like effects. Moreover, the alterations of the transcriptome induced by an HDAC inhibitor were very similar to those induced by the antidepressant fluoxetine [21]. A related study investigated promoter chromatin regulation by chromatin immunoprecipitation-chip assays in the nucleus accumbens of chronically stressed mice. Many of the stress-induced changes were reversed by treatment with imipramine, and the resultant pattern exhibited a surprising similarity to that of stress-resilient mice [99].

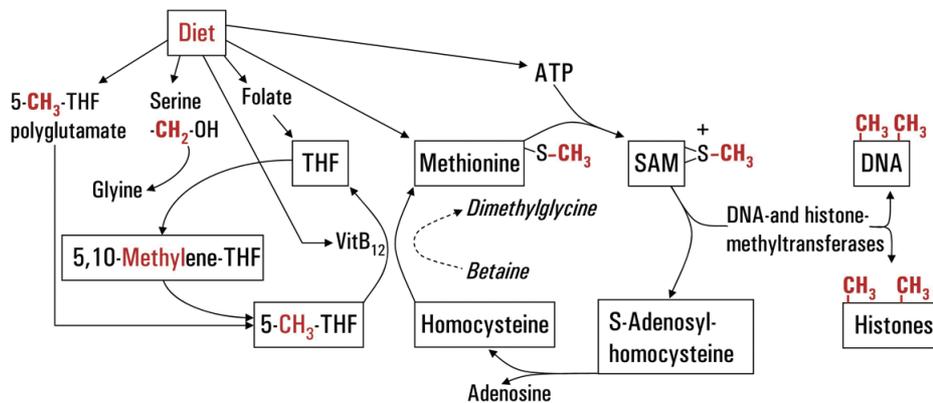


Fig. 1. One carbon cycle linking to epigenetic modifications of DNA and histones. Methylation of DNA, histones and other molecules in the cell is orchestrated by an array of enzymes controlling the turnover of the involved metabolites. Options for (auxiliary) epigenetic treatment focus on manipulation of the enzymatic activity of DNA- and histone-methyltransferases, as well as of the levels of folate, SAM and vitamin B12. The remethylation of homocysteine via betaine occurs in liver and kidney, but not in the central nervous system (dashed arrow). THF, tetrahydrofolate; SAM, S-adenosylmethionine.

HDACIs have also been shown to impact on DNA methylation at schizophrenia-relevant promoters, via decreasing the activity of DNMTs, very similar to the effects of direct DNMT inhibitors [47]. Yet other research directions explore the possibility of manipulating the available pool of methyl donors. For example, S-adenosyl-methionine (SAM, Fig. 1), an important methyl donor in cellular processes, has been evaluated for potential antidepressant effects with promising results [58]. In addition, folate and vitamin B12 status, two other important components of the one carbon cycle, have been linked to the incidence of depression and to the success of antidepressant treatment [18,63,69]. Moreover, genetic variants of the enzyme that catalyses the conversion of 5,10 methylene tetrahydrofolate to 5-methyl-tetrahydrofolate (Fig. 1) have been linked to depression [18,69]. Thus, genetic variation of the respective enzymes will have to be considered when assessing the impact of treatment regimes that target the one carbon pathway [14].

While all these developments are encouraging, it needs to be considered that most of the epigenetic drugs exert pleiotropic effects and are thus prone to exhibit severe side effects [22,34]. For psychiatric diseases in general, it will be necessary to develop and test drugs directed towards more specific epigenetic mechanisms. Together with advances in understanding the specific and probably individual epigenetic processes in disease, this may allow formulation of personalized epigenetic treatment, possibly as co-medication, optimizing efficacy and minimizing side effects.

In PTSD in particular, side effects may be tolerable or even less pronounced, because treatment in many cases

is only short-term. It is conceivable that an immediate posttraumatic pharmacological intervention, sometimes referred to as secondary prevention, might prevent the onset of PTSD symptoms. In the majority of patients, PTSD symptoms appear weeks after the traumatic experience, and early intervention prior to emergence of clinical symptoms may be an opportunity also for treatment with epigenetic drugs that interfere with programming of PTSD symptoms.

There is a limited number of studies exploring the possibility of secondary treatment in PTSD: Adrenoreceptor antagonists like the conventionally used anti-hypertensive propranolol have been found to prevent or at least to mitigate the onset of PTSD-typical re-experiencing symptoms like flashbacks and intrusions if applied in the immediate aftermath of a traumatic event [33,94]. Many authors have suggested that propranolol and other anti-adrenergic drugs to impede memory formation thereby preventing the onset of tantalizing flashbacks in predisposed individuals. This notion however is not unanimously accepted and some authors have questioned the therapeutic and/or preventive effects of adrenoreceptor antagonists in PTSD [61]. Furthermore, low dosed glucocorticoid administration has been reported to reduce the risk of developing PTSD after a traumatic event [78]. In addition, morphine is reported to reduce the risk of subsequent development of PTSD after serious injury [39]. Finally, there is also evidence from a mouse model that post stress preventive treatment with the SSRI sertraline reduces the development of PTSD-like behavior [51]. Taken together, mounting evidence supports the concept of preventive

treatment of PTSD in general, and the field would benefit from discovery and development of drugs targeting epigenetic mechanisms.

The epigenetic therapy in PTSD is probably not limited to preventive treatment but may also extend to treatment of already developed PTSD. Antidepressants and mood stabilizers are frequently used in PTSD therapy [2,6]. The epigenetic mode of action of some of these drugs may contribute to their overall effect [70]. It should be noted, though, that while SSRIs have been shown to reduce PTSD symptoms, treatment results are not fully convincing with about 40% of SSRI-treated PTSD patients not responding at all and only 20–30% of them reaching full remission [6]. Certain psychotherapeutic strategies have been shown to be effective in PTSD sufferers [26], but they are characterized by a protracted onset of improvement.

A substantial portion of individuals at all ages is prone to develop PTSD if exposed to traumatizing events. We are beginning to understand the biochemical mechanisms that are translating these experiences into changes of gene activity and their physiological and behavioral consequences. We hope this better understanding of underlying pathology will ultimately result in better treatment options for these patients.

Thus, there is urgent need for the development of PTSD-specific medication, to which epigenetic therapy could make an important contribution.

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