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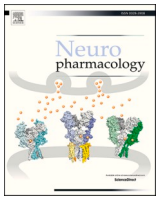

Glucocorticoid-based pharmacotherapies preventing PTSD

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ABSTRACT

Posttraumatic stress disorder (PTSD) is a highly disabling psychiatric condition that may arise after exposure to acute and severe trauma. It is a highly prevalent mental disorder worldwide, and the current treatment options for these patients remain limited due to low effectiveness. The time window right after traumatic events provides clinicians with a unique opportunity for preventive interventions against potential deleterious alterations in brain function that lead to PTSD. Some studies pointed out that PTSD patients present an abnormal function of the hypothalamic-pituitary-adrenal axis that may contribute to a vulnerability toward PTSD. Moreover, glucocorticoids have arisen as a promising option for preventing the disorder's development when administered in the aftermath of trauma. The present work compiles the recent findings of glucocorticoid administration for the prevention of a PTSD phenotype, from human studies to animal models of PTSD. Overall, glucocorticoid-based therapies for preventing PTSD demonstrated moderate evidence in terms of efficacy in both clinical and preclinical studies. Although clinical studies point out that glucocorticoids may not be effective for all patients' subpopulations, those with adequate traits might greatly benefit from them. Preclinical studies provide precise insight into the mechanisms mediating this preventive effect, showing glucocorticoid-based prevention to reduce long-lasting behavioral and neurobiological abnormalities caused by traumatic stress. However, further research is needed to delineate the precise mechanisms and the extent to which these interventions can translate into lower PTSD rates and morbidity.

1. Introduction

Posttraumatic Stress Disorder (PTSD) is a highly prevalent mental disorder that some people develop after experiencing a traumatic event. The PTSD diagnosis requires the presence of one or more clusters of symptoms after trauma exposure that persist for at least one month and could comprise: intrusive thoughts, avoidance of trauma reminders, negative alterations in cognition, mood, and arousal, and hyperreactivity (American Psychiatric Association, 2013). It is reported that more than 70% of the worldwide population experience a traumatic event at least once in their lives; yet only a subset of individuals consequently develop PTSD, thus, suggesting that inter-individual differences can confer vulnerability and resilience toward the effects of severe stressors. The lifetime prevalence of PTSD ranges from 1.3 to 12.2% depending on the social background, country of origin, and trauma type, with rates above 18% for war veterans and up to 39% in sexually abused women (Dohrenwend et al., 2006; Shalev et al., 2017; Kessler et al., 2014; Möller et al., 2014).

There is a range of approaches available to treat PTSD including both pharmacotherapy and psychotherapy. First-line treatments of PTSD are forms of psychotherapy, mainly cognitive–behavioral therapy (CBT) and exposure therapy, but unfortunately, the ratio of patients that do not fully respond to these approaches is as high as 50% (Kar, 2011).

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Abbreviations

18F-FDG	18F-fluorodeoxyglucose
ACTH	Adrenocorticotropin hormone
AMT	Autobiographical memory retrieval task
ASR	Amplitude of the startle response
AVP	Arginine vasopressin peptide
BDNF	Brain-derived neurotrophic factor
BLA	Basolateral amygdala
CBT	Cognitive–behavioral therapy
CRH	Corticotropin-releasing hormone
CRHR1	CRH type 1 receptors
BOLD	Blood oxygenation level-dependent
DEX	Dexamethasone
EPM	Elevated plus maze
fMRI	Functional magnetic resonance imaging
GABA	Gamma-aminobutyric acid
GR	Glucocorticoid receptors
HPA	Hypothalamus-pituitary-adrenal
HRQL	Health-related quality of life
ICU	Intensive care unit
MR	Mineralocorticoid receptors
NF-κB	Nuclear factor-κB
PET	Positron emission tomography
PPM1F	Protein phosphatase 1F
PSD-95	Postsynaptic density-95
PTSD	Posttraumatic stress disorder
PVN	Hypothalamic paraventricular nucleus
SNP	Single nucleotide polymorphism

Currently, the use of antidepressants as therapeutic agents is widely spread in clinical settings, although their efficacy is generally smaller compared to the observed in psychotherapy-based interventions (Lee et al., 2016). Since a substantial proportion of patients present symptoms or maintain the PTSD diagnosis after therapy (Steenkamp et al., 2015; Stein et al., 2006; Zohar et al., 2002), novel therapeutic strategies should be developed to address this important gap in the prevalence of PTSD.

Epidemiological findings have identified that certain stressors are more likely than others to result in a PTSD diagnosis, such as sexual abuse or car accidents (Perkonigg et al., 2000). Thus, the possibility of preventing PTSD development is gaining relevance due to the prompt identification of risky situations. In this line, prevention strategies are classified as primary, secondary, or tertiary (Campion et al., 2020). Primary prevention strategies focus on reducing the risk of exposure to trauma or decreasing its pathogenicity. Secondary prevention strategies are used once the traumatic exposure has occurred and regardless of the degree of symptoms, but before the onset of a full PTSD diagnosis. Tertiary prevention is focused on PTSD patients, and interventions are given along with treatments to hamper disease progression and disability once the diagnosis has been established (Campion et al., 2020). Therefore, secondary prevention strategies offer the opportunity to delay or avoid the onset of the disease once a traumatic exposure has occurred, acting as powerful agents that might hamper the progress of the consequences of stress exposure. Psychological secondary prevention interventions were found to have positive evidence supporting their use, although no universal consensus regarding their effectiveness has been established, and their use is not routinely recommended (Bisson et al., 2021; Roberts et al., 2019). Studies that have tested pharmacotherapies, including beta-blockers or benzodiazepines, as preventive interventions for PTSD show conflicting results with little or no contrasted full efficacy for the available treatments (Bertolini et al., 2022; Sijbrandij et al., 2015).

Given the traumatic nature of the disease, alterations in the stress response via Hypothalamus-Pituitary-Adrenal (HPA) axis responsiveness are likely to be at the core of PTSD vulnerability.Thereby the modulation of glucocorticoid levels in the moment of the traumatic experiences could protect against its development. Classical ideas in the field point at glucocorticoids as mediators of stress-induced impairments. Novel research has arisen proving the efficacy of glucocorticoid administration in the aftermath of trauma as a plausible strategy for secondary prevention against PTSD. The present work reviews clinical and preclinical literature on glucocorticoid administration's efficacy in the prevention of the deleterious consequences of trauma.

2. Glucocorticoids dynamics in PTSD

Traumatic experiences typically trigger a stress response involving the fast-acting autonomic nervous system and the slow-acting HPA axis. The final products of the HPA axis, glucocorticoids, are released into the bloodstream from the adrenal glands (Herman, 2013). Glucocorticoids (i.e., cortisol and corticosterone being the most prominent ones in humans and rodents, respectively) promote brain and body functions that facilitate adaptation and recovery when individuals face stressful challenges. Specifically, their life-sustaining functions include the mobilization of substrates for energy metabolism, the suppression of primary immune and inflammatory responses, and the modulation of cognitive processes (de Kloet et al., 2005; Sandi, 2011, 2013; Ulrich-Lai and Herman, 2009).

Upon stress, the activation of the HPA axis elicits the release of corticotropin-releasing hormone (CRH) from the hypothalamic paraventricular nucleus (PVN). CRH reaches the anterior pituitary via the hypophysial portal vessels where it binds CRH type 1 receptors (CRHR1), promoting the synthesis of pro-opiomelanocortin, the precursor of adrenocorticotropin hormone (ACTH). ACTH is released in the systemic circulation and stimulates the release of cortisol by the adrenal cortex. In parallel to CRH release, the vasopressin peptide (AVP), whose main role is to maintain the proper volume of water in the extracellular body fluid, is also released. Indeed, when AVP is colocalized with CRH in the parvocellular neurons of the PVN, AVP amplifies its action on ACTH release, a process that could play an important role in sustaining chronic stress effects (Ulrich-Lai and Herman, 2009). In addition, vasopressin acts in the brain via V1, V2 and V3 receptors involved in various aspects of social behaviour (Wersinger et al., 2002), as well as in emotional and cognitive processing (Wersinger et al., 2002).

Corticosteroids exert their functions by binding to the mineralocorticoid receptors (MR) and glucocorticoid receptors (GR) which act via genomic and non-genomic mechanisms (Kloet and Joëls, 2020; Popoli et al., 2011; Reul and de Kloet, 1985). In the brain, MR are mostly expressed in neurons from limbic areas, but GR are found ubiquitously, in both glial cells and neurons, with the highest number in the PVN and hippocampus. MR are involved in the appraisal of novel situations and adaptation processes during the onset of the stress response, while GR, having a 10-fold lower affinity for corticosterone, play a crucial role in the stress response lingering after exposure to an actual stressor. In particular, it facilitates the recovery from stress experiences by mobilizing energy resources and by terminating the stress reaction via negative feedback on multiple nodes of the HPA axis (Kloet and Joëls, 2020; Sandi, 2011, 2013). MR and GR act in a coordinated manner when facing a stressor (de Kloet et al., 2019; de Quervain et al., 2019). MR act rapidly at the onset of stress, initiating the stress response by selecting an adequate coping mechanism through non-genomic mechanisms. Then,

upon the termination of stress, MR-GR and GR-GR dimers and GR monomers promote adaptation to future stressors through genomic actions that facilitate recovery, rationalisation and contextualisation of the stress response (de Kloet et al., 2019).

It was first hypothesized that PTSD patients would respond to trauma with high cortisol release, given the sustained urinary catecholamine levels found in these patients (Kosten et al., 1987; Yehuda, 2002). However, an early study conducted on Vietnam war veterans reported low cortisol levels in PTSD subjects compared to other psychiatric patients (Mason et al., 1986). This first report triggered substantial interest. As commented by the authors, "… this finding of low, stable cortisol levels in PTSD patients is especially noteworthy, first because of the overt signs of anxiety and depression, which would usually be expected to accompany cortisol elevations, and second because of the concomitant chronic increase in sympathetic nervous system activity". Yet, such observations were not confirmed in later reports (Elzinga et al., 2003; Maes et al., 1998), indicating substantial variability in the outcome of cortisol measurements across studies. Indeed, there are important differences in the cortisol levels observed in PTSD studies. Several factors, including the type of samples collected for cortisol measurement and the circadian time of sample collection, sex, circadian hormonal fluctuations, the presence of comorbidities, and tobacco consumption are known to influence HPA activity (Meewisse et al., 2007; Oyola and Handa, 2017; Rohleder and Kirschbaum, 2006; Van Den Heuvel et al., 2019; Yehuda et al., 2005). Of note, early-life trauma exposure may especially contribute to develop a PTSD phenotype in adulthood by inducing changes in brain development. Although the literature is less clear when it comes to single trauma exposure during childhood, children under chronic abuse develop an HPA axis sensitization that may contribute to pathology during adulthood (Pratchett and Yehuda, 2011). An important factor that may contribute to the discrepancies in the reported results is the choice of the appropriate control group across studies. While some trials use non-trauma-exposed controls, others contemplate trauma-exposed controls without PTSD(Klaassens et al., 2012; Morris et al., 2012). In addition, the life cycle at the moment of trauma seems also to be an important factor affecting cortisol levels. In one meta-analysis of 47 articles, the lowest cortisol levels at awakening were found in patients that were exposed to trauma during childhood compared to adulthood (Morris et al., 2012). Moreover, this meta-analysis pointed out that the strength and reliability of findings examining cortisol levels in PTSD patients are influenced by several factors, therefore particular attention should be paid to the study design.

The evaluation of glucocorticoid levels in response to a challenge -which reflects HPA reactivity- is biologically relevant. The most consistent finding among PTSD patients is an important suppression of cortisol in response to dexamethasone (DEX), which denotes an enhanced negative feedback inhibition of the HPA axis (Lange et al., 2005; Newport et al., 2004; Yehuda et al., 2002, Yehuda, 2009b). The enhanced negative feedback is supposed to be the consequence of a greater GR sensitivity, as suggested by the increased GR responsiveness in response to DEX administration (Daskalakis et al., 2013a; Yehuda et al., 2009). However, other mechanisms, such as a stress-induced increased CRH release from the amygdala (Makino et al., 1999), or a reduced ability of the adrenals to produce cortisol (Heim et al., 2000), might also impair the glucocorticoid negative feedback.

Traditionally, it was assumed that low cortisol levels in association with PTSD were a consequence, rather than a cause, of trauma. However, data from recent studies suggest that this feature may reflect a pre-existing vulnerability trait as a consequence of epigenetic modifications induced by early-life adversity. One of the first remarkable observations in support of the existence of a priori vulnerability captured by cortisol responsiveness was the finding that individuals displaying low cortisol levels in the emergency room (ER), immediately after the traumatic event, were the ones eventually developing PTSD (Yehuda et al., 1998). In line with this finding, a recent study using a powerful machine learning analysis showed that decreased levels of cortisol collected at the ER following the trauma accurately predict a major risk of non-remitting PTSD later on, and this finding was stronger when the subject had a history of childhood trauma (Galatzer-Levy et al., 2017). These results suggest glucocorticoid-based therapy in the aftermath of trauma might be relevant for preventing the development of PTSD, in particular in subjects who experienced childhood trauma.

Another important field of research for the study of PTSD is genetics, due to a specific genetic background that might explain, at least partially, the altered HPA axis responsiveness associated with PSTD (Yehuda et al., 2011). In particular, the phistory of PTSD inone parent is linked to an increased risk for the development of PTSD in trauma-exposed offspring. In a study analyzing the offspring of Holocaust survivors, low cortisol was found in the offspring of PTSD subjects and was linked to a major vulnerability to developing PTSD in life (Yehuda and Bierer, 2007). Recently, a follow-up study, using the same database, elegantly showed that low glucocorticoid levels in the adult offspring of Holocaust survivors were associated with differentially expressed genes, in particular, enriched for glucocorticoid-regulated genes and immune pathways (Daskalakis et al., 2020).

Several studies on candidate genes point out the presence of single nucleotide polymorphisms (SNP) in PTSD patients that are related to GR function or measures of GR function, directly or via the experience of trauma during childhood (Binder et al., 2008; Mehta et al., 2011; Van Zuiden et al., 2012). For example, in a recent meta-analysis of HPA-related genes from both traditional SNP and new gene-level methods, a significant relationship between PTSD and *NR3C1* (which encodes for GR) and *FKBP5* (a co-chaperon protein regulating the GR sensitivity) at the gene level was reported (Sheerin et al., 2020). Moreover, the gene level meta-analysis of *CRHR1* was also significant when associated with PTSD, but the result was not equally robust as it did not survive multiple testing corrections (Sheerin et al., 2020). Furthermore, allelic variants of *FKBP5* have been linked to biologically distinct PTSD subtypes about GR function (Mehta et al., 2011). Overall, these findings suggest that HPA axis alterations may be critical in determining PTSD pathophysiology and underscore the view that low cortisol levels constitute a pre-existing risk factor to develop PTSD, probably induced by early-life adversity, instead of a consequence of the trauma. Thus, research on the HPA axis profile before and in the aftermath of a trauma is still ongoing and will eventually shed light on neurobiological mechanisms underpinning the preventive response of glucocorticoids.

In addition, the characterization of specific biobehavioral phenotypes and HPA axis parameters among PTSD patients and/or individuals at risk following trauma might provide an opportunity for clinical intervention in this field. One of the main roles of glucocorticoid stress hormones is to modulate the mnemonic processing of emotionally arousing experiences (de Quervain et al., 2016; Sandi, 2011, 2013; Sandi and Pinelo-Nava, 2007). Years of research have pointed out that glucocorticoids exert divergent effects depending on the specific memory process (timing) -such as consolidation, retrieval, extinction, and reconsolidation- as well as their context of occurrence in information processing (de Quervain et al., 2009; Joëls et al., 2006). Specifically, early work showed that acute administration of corticosteroids enhances memory consolidation of emotionally relevant experiences (Sandi et al., 1997; Sandi and Rose, 1994a, 1994b), but impairs memory retrieval of already stored information (de Quervain, 1998). Likewise, impaired cognitive function is typically found in conditions associated with elevated glucocorticoids, which might occur when individuals are exposed to traumatic or repeated stressful events (McEwen, 2000; Sandi, 2004). Interestingly, the intracranial administration of the selective GR antagonist mifepristone given right before or after the first session of a Morris water maze task disrupts recall in the following session, while the same approach before session 2 does not affect recall, proving a direct effect on contextual memory consolidation rather than in acquisition or retrieval of memories (Oitzl and de Kloet, 1992).

Specifically, glucocorticoids promote the consolidation of contextual

features of fear memories in the dorsal hippocampus (Cordero et al., 1998, 2002; Cordero and Sandi, 1998) and emotional traits in the amygdala and ventral hippocampus through synergistic actions with catecholamines (Roozendaal et al., 2004, 2009). Imbalances in neurotransmitter levels can result in the "over-consolidation" of traumatic experiences. The persistence of a hyperactive amygdala could explain the exaggerated response of fear response, as well as explain symptoms of PTSD such as hypervigilance and hyperarousal (Rauch et al., 2000). Moreover, glucocorticoid administration also enhances fear extinction (Galatzer-Levy et al., 2017; Jovanovic et al., 2011; Merz et al., 2017; Sawamura et al., 2016; Yang et al., 2006). In particular, DEX administration has been shown to enhance extinction learning and its retention of the learned fearful memory in both rodents and humans (Jovanovic et al., 2011; Sawamura et al., 2016; Yang et al., 2006), along with inducing a transient suppression of the HPA axis. By modulating different memory processes, glucocorticoids can contribute to reducing high fear responses, by both supporting fear extinction and reducing the retention of aversive memories (Sandi, 2011, 2013; de Quervain et al., 2016), or facilitating contextual previously consolidated memory processes by acting on the hippocampus (Bohus and Lissák, 1968; Cai et al., 2006). Although glucocorticoids have typically shown to have a facilitating role in learning, glucocorticoids exert opposing roles on memory consolidation depending on the timing of stress and context of retrieval (Kirschbaum et al., 1996). High cortisol levels right before the acquisition of a learning task impair the consolidation of declarative memories (Kirschbaum et al., 1996); whereas it can be facilitated when stress exposure takes place at the same time and in the same context of the acquisition (Joëls et al., 2006).

One of the theoretical bases supporting the use of glucocorticoids after traumatic stress arises from their capacity to alter memory consolidation, impair memory retrieval, enhance extinction memories, and enhance fear extinction after a context-dependent fear memory reactivation (de Quervain et al., 2009; Cai et al., 2006). Importantly, these effects are highly dependent on the timing of glucocorticoid administration and their convergence with noradrenaline actions in the amygdala and hippocampus (de Quervain et al., 2009). This evidence, accompanied by data suggesting that PTSD patients have disruptions in HPA function, has led to evaluate the efficacy of glucocorticoid administration at different time windows after the trauma.

3. Clinical evidence

3.1. Prevention of PTSD with glucocorticoids

Efforts have been made to test whether glucocorticoid therapy could be beneficial for PTSD prevention (Table 1). In August 2022, we identified 9 published studies that used glucocorticoids as preventive therapy for PTSD, of which 8 used hydrocortisone and 1 DEX. Hydrocortisone (cortisol) is the naturally occurring glucocorticoid in man, short-acting (8–12h), and usually devoid of mineralocorticoid activity because of its enzymatic degradation in target tissues. DEX is a long-acting (>36h) synthetic corticosteroid with a 50-fold potency than hydrocortisone, acting as a GR agonist with no mineralocorticoid activity. Cortisol binds to the glucocorticoid-preferring MR in the brain and heart, which does not bind DEX.

Two studies with hydrocortisone (Schelling et al., 2004; Weis et al., 2006) and one with DEX (Kok et al., 2016) tested whether PTSD could be prevented in high-risk patients undergoing a planned cardiac surgery with cardiopulmonary bypass. Participants were on average around 70 years old and mostly men. For hydrocortisone studies, a placebo or drug (100 mg bolus + 10 mg/h) was administered parenterally as an infusion starting before surgery and tapered over 3 days. Posttraumatic symptoms and health-related quality of life (HRQL) were assessed at 6 months. In both studies, hydrocortisone was beneficial for decreasing PTSD severity and in one study it also improved quality of life (Weis et al., 2006). Hydrocortisone was also related to lower IL-6 levels, shorter intensive care unit (ICU) stay, and lower vasopressor (noradrenaline) doses during surgery. Further testing showed that hydrocortisone was more effective in patients showing multiple sub-symptom categories and that prior PTSD memories increased the risk for traumatic memories after surgery. In the study with the largest number of participants from all the reviewed studies (>500 per arm), DEX was given parenterally as a single dose (1 mg/kg) before surgery, PTSD, HRQL, and depressive symptoms were evaluated at one variable timepoint (18–48 months) (Kok et al., 2016). No differences were found for PTSD, depressive symptoms, or HRQL. However, subgroup analyses showed that DEX may improve PTSD and depressive symptoms in women.

Two studies investigated whether hydrocortisone could improve PTSD outcomes in septic shock patients (Denke et al., 2008; Schelling et al., 2001). Demographic data is not available for one study (Denke et al., 2008), and in the other, the sample consisted mostly of men around 50 years old (Schelling et al., 2001). For both studies, hydrocortisone was administered parenterally during ICU stay at variable intervals and doses (0.18 mg/kg/h or 50 mg each 6h) with 6 additional days of tapering. No differences in PTSD symptom severity were found (Schelling et al., 2001) or reported (Denke et al., 2008). Nevertheless, lower PTSD rates for the hydrocortisone group (1/9 hydrocortisone, 7/11 placebo) were found in one study (Schelling et al., 2001). Hydrocortisone was also related to lower and shorter doses of vasopressor therapy (noradrenaline) and better clinical outcomes in the ICU (Schelling et al., 2001).

Four studies focused on hydrocortisone interventions shortly after traumatic injury (Carmi et al., 2022; Delahanty et al., 2013; Shaked et al., 2021; Zohar et al., 2011a). The study participants were mostly men and around 35 years old. Amnesic patients, seriously injured or needing surgical intervention were discarded. Two studies selected specifically patients that had a high risk of dissociation or with prominent posttraumatic symptoms (Carmi et al., 2022; Delahanty et al., 2013). Hydrocortisone was administered parenterally in three studies as a single dose (100–140 mg) within 6 h after trauma (Carmi et al., 2022; Shaked et al., 2021; Zohar et al., 2011a) and orally (20 mg/12 h for 10 days plus tapering) starting within 12 h after trauma (Delahanty et al., 2013). PTSD symptoms were assessed at variable time points after trauma. In one study, hydrocortisone resulted in a large reduction of PTSD symptom severity at the 2-week and 3-month assessments, while PTSD rates were not significantly different among groups (3/8 placebo-, 1/9 hydrocortisone-cases). Also, hydrocortisone improved anxiety and depressive symptoms (Zohar et al., 2011a). However, a follow-up study failed to replicate these findings but found that hydrocortisone was beneficial for PTSD severity if patients were clustered by trauma time (at night versus at day) (Carmi et al., 2022). In another study, hydrocortisone reduced overall PTSD symptoms, but this effect was moderated by prior mental health treatment, as treatment was most effective in patients not having any prior mental health care (Delahanty et al., 2013). In the last study, no differences were detected for PTSD symptoms at the 1-month assessment, but subgroup analyses showed that hydrocortisone resulted in worse clinical outcomes and greater PTSD symptoms in the group with low cortisol at admission (9.5 μg/dl cutoff) (Shaked et al., 2021).

Meta-analyses and systematic reviews have shown that hydrocortisone is beneficial for the prevention of PTSD onset and PTSD intensity when assessing outcomes at the nearest point to 3 months post-intervention or at the study endpoint. However, no evidence for hydrocortisone benefits was observed if outcomes were assessed specifically at 3 months or more than 6 months post-intervention (Amos et al., 2014; Astill Wright et al., 2019; Bertolini et al., 2022; Bisson et al., 2021; Kothgassner et al., 2021; Sijbrandij et al., 2015). One meta-analysis that included studies using universal prevention (in all the exposed) and indicated prevention (exposed with symptomatology) found moderate quality evidence for hydrocortisone efficacy for PTSD intensity (4 studies, RR = 0.17, CI (95%) 0.05–0.56) with a number needed to treat

Table 1

Selected characteristics of preventive studies using glucocorticoids for PTSD. All studies were randomized, two-arms, double-blind and placebo-controlled, except for Schelling et al. (2004) single-blind and compared against standard therapy. BDI= Beck Depression Inventory, bol = bolus, C = control, CAPS= Clinician-Administered PTSD Scale, CES-D = Center for Epidemiological Studies-Depression, d = day, h = hour, ICU = intensive care unit, IV = intravenous, mo = month, n.s. = not specified, NA = noradrenaline, PDS= Posttraumatic Stress Diagnostic Scale, PO = oral, PTSS-10 = Posttraumatic Stress Symptom 10-Question Inventory, QOL = quality of life, SCID-IV= Structured Clinical Interview for the DSM-IV, SD = single dose, SF-36 = Short Form Health Survey 36-item, SRIP= Self Rating Inventory for Posttraumatic stress disorder, TX = treatment, VAS = visual analogue scale, w = week.

ID		Demographics				Drugs			Assessments		Outcomes	
First Author	Year	Age	Gender (men/ total)	part per arm (placebo, TX)	Trauma type (type of patient)	Intention	Medication (route)	Dosage	Time points of outcome assessment	Instruments	Outcomes	Other outcomes
Schelling	2004	C 69 (64–75), TX 70 (64–75)	C 20/26, TX 15/ 22	22, 26	Cardiac surgery + ICU stay (high-risk)	Preventive before trauma	Hydrocortisone (IV)	bol (100 mg) + 24 h (10 mg/h) + tapering 3 d	6 mo	PTSS-10	Lower PTSD symptoms in hydrocortisone. Subgroup: hydrocortisone benefits patients with multiple symptom categories	IL-6 is lower in hydrocortisone
Weis	2006	C 69 (63–73), TX 68 (63–72)	C 9/14, TX 10/ 14	14,14	Cardiac surgery + ICU stay (high-risk)	Preventive before trauma	Hydrocortisone (IV)	bol (100 mg) + 24 h (10 mg/h) + tapering 3 d	6 mo	PTSS-10 mod, SF-36	Lower PTSD symptoms in hydrocortisone. PTSD rate 1/14 hydrocortisone vs 3/14 placebo ($p > 0.05$)	Better QOL, shorter ICU stay, lower NA doses, lower IL-6 in hydrocortisone
Kok	2016	C 69.6 (63.4–76.2), TX 68.4 (62.2–75.9)	C 435/ 561, TX 443/564	564, 561	Cardiac surgery + ICU stay (high-risk)	Preventive before trauma	Dexamethasone (IV)	SD (1 mg/kg)	18 mo–48 mo	SRIP, BDI, SF-36	No differences in PTSD symptoms or rates. Subgroup: women's prevalence was lower in dexamethasone 4/52 vs placebo 16/66	No differences in depressive symptoms. Subgroup: hydrocortisone women had lower rates of depression
Schelling	2001	C 55 (25–75) TX 48 (23–76)	C 5/6, TX 3/6	11, 9	Septic shock + ICU stay (high-risk)	Preventive during trauma	Hydrocortisone (IV)	bol (100 mg) + 6 d (0.18 mg/kg) + tapering (14–35 d)	31 mo (21–49)	SCID-IV, PTSS-10 mod	No differences in PTSD symptoms. PTSD rates 1/9 hydrocortisone vs 7/11 placebo	Lower NA doses in hydrocortisone
Denke	2008	n.s.	n.s.	9, 9	Septic shock + ICU stay (high-risk)	Preventive during trauma	Hydrocortisone (IV)	5 d (50 mg q.6 h) + 6 d tapering	12 mo	PTSS-10, SF-36	PTSD symptoms were not reported. No differences in PTSD rate	
Zohar	2011	C 34 (22–62), TX 36 (20–62)	C 6/8, TX 3/9	8, 9	Traffic accident, work accident (excl. seriously injured)	Preventive after trauma	Hydrocortisone (IV)	SD (100–140 mg)	Before, 2 w, 1 mo, 3 mo	CAPS, VAS	Lower PTSD symptoms in hydrocortisone at 2 w and 3 mo. PTSD rates 1/9 hydrocortisone vs 3/8 placebo ($p > 0.05$)	Lower anxiety and depression in hydrocortisone
Carmi	2022	C 40.4 (12.6), TX 38.1 (12.5)	C 22/45, TX 24/ 51	45, 51	Traffic accident, work accident, violence (excl. seriously injured)	Preventive after trauma	Hydrocortisone (IV)	SD (100–140 mg)	0, 2 w, 1 mo, 3 mo, 8 mo, 13 mo	CAPS. VAS	No differences in PTSD symptoms or rates. Subgroup: trauma time (at night vs at day); placebo night had higher symptoms than placebo day + hydrocortisone night had lower PTSD prevalence than hydrocortisone day	No differences
Delanthy	2013	C 33.8, TX 27.2	C 21/33, TX 21/ 31	33, 31	Traffic accident, falls (excl. seriously injured, incl. high risk of dissociation)	Preventive after trauma	Hydrocortisone (PO)	10 d (40 mg/ d) + 6 d tapering	1 mo, 3 mo	CAPS, CES-D self-report, SF-36	Lower PTSD symptoms in hydrocortisone. Subgroup: hydrocortisone benefits mostly patients without a psychiatric history	Better QOL and lower depressive symptoms in hydrocortisone
Shaked	2021	n.s.	n.s.	39, 38	Traffic accident	Preventive after trauma	Hydrocortisone (IV)	SD (100 mg)	1 mo	PDS	No differences in PTSD symptoms. Subgroup: Hydrocortisone low cortisol group had greater PTSD symptoms	

of 7–13 patients to prevent PTSD in one patient (Amos et al., 2014). However, studies were found to be at high risk of bias due to differential dropouts and small sample sizes. Other meta-analysis found that hydrocortisone may reduce the chances of experiencing PTSD when used as universal prevention (2 studies, RR = 0.23, CI (95%) 0.06–0.96), but this finding was labeled as unclear evidence due to a high risk of bias given the imprecise effect estimates and small sample sizes (Bertolini et al., 2022). Other systematic reviews and meta-analyses have found that hydrocortisone is better than placebo for preventing PTSD onset and intensity by combining universal and indicated prevention approaches (Astill Wright et al., 2019; Bisson et al., 2021; Sijbrandij et al., 2015). In addition, one meta-analysis (Kothgassner et al., 2021) pooled studies that used hydrocortisone in a preventive and curative context and found evidence for its efficacy for PTSD symptoms (8 studies, d = 0.96 CI (95%) 0.22 to 1.69) and lower PTSD incidence (5 studies, log RR = 0.85, CI (95%) 0.12 to 1.59). However, further analyses showed that the benefits were constrained to studies using hydrocortisone in a preventive setting and with a parenteral route of administration.

Overall, these analyses show the possible effect of hydrocortisone administration on the prevention of PTSD after severe stress. However, the reviewed studies and their conclusions should be weighed against their limitations. Most of the available trials have small sample sizes, different hydrocortisone dosages, variable timings for treatment efficacy assessment and different scales used for PTSD characterization and severity. Moreover, the samples in the studies are highly heterogeneous in terms of age, trauma history, and the nature of the traumatic experience. Potential sources of bias include high attrition rates and differential dropouts that are more likely in the treatment group. Notably, some studies reported that hydrocortisone was related to better clinical outcomes, shorter ICU stays, and lower noradrenaline doses, suggesting an alternative explanation for the increased PTSD risk in placebo groups (Schelling et al., 2001; Weis et al., 2006). Further, these studies pointed at relevant variables to consider in future research, such as a history of psychopathology and trauma, sex as a biological variable, endogenous cortisol levels, and concomitant drug therapy since all of these variables appear to be modulators of the hydrocortisone treatment effects.

3.2. Treatment of PTSD with glucocorticoids

Studies exploring hydrocortisone as a curative intervention in patients with a PTSD diagnosis show mixed results (Table 2). One study administered a single bolus of hydrocortisone (4 mg/kg) after memory reactivation in a sample of men with combat-related PTSD and found a temporary reduction of PTSD symptoms (1-week post-treatment) that was not maintained over time (1-month post-treatment) (Surís et al., 2010). In other two studies with a crossover design oral hydrocortisone was administered for 1 month (10–30 mg/d) to patients with PTSD secondary to heterogeneous traumas (Aerni et al., 2004; Ludäscher et al., 2015). One study with 3 patients showed some positive effects for the hydrocortisone-treated group over the frequency and intensity of reexperiencing symptoms and physiological distress (Aerni et al., 2004), but the one including a larger sample found null results (Ludäscher et al., 2015). Two other studies used hydrocortisone to augment exposure therapy outcomes in men with combat-related PTSD. Participants were given 30 mg of oral hydrocortisone shortly before the exposure therapy session and PTSD outcomes were assessed at variable intervals (Yehuda et al., 2015; Lehrner et al., 2021). One of the studies found lower PTSD symptoms in the hydrocortisone group, especially in patients with greater PTSD lifetime severity (Yehuda et al., 2015). The other study found beneficial effects of exposure therapy over time but no effects for hydrocortisone, although in subgroup analyses patients with post-concussive symptoms and receiving hydrocortisone had lower hyperarousal symptoms (Lehrner et al., 2021). Two other small studies explored the efficacy of mifepristone, progesterone, glucocorticoid, and androgen receptor antagonist. A single oral dose (1800 mg) before memory reactivation did not result in significant differences in physiological responses or PTSD symptoms, but daily doses (600 mg/d) reduced PTSD symptom intensity and clinical severity (Golier et al., 2012; Wood et al., 2015).

It is especially relevant to overcome the heterogeneity in the reported results on treatment efficacy with glucocorticoid-based drugs. This heterogeneity may arise from sociodemographic conditions, traumatic stress sources, routes of administration for hydrocortisone, and different dosages employed, which differ among studies. Although limited, the data provided suggests that treatment with hydrocortisone might result beneficial to a specific population of PTSD patients that present specific conditions, such as the war-related nature of the trauma or a greater lifetime severity of PTSD symptoms. Also, the reactivation of traumatic memories in a clinically controlled environment lacks strong contextual features, which may result in an insufficiently recruited traumatic memory. The administration of glucocorticoids for an incompletely reactivated memory may result in treatment efficacy that is lost when the patient is transferred to their normal environment. Therefore, the recruitment of the contextual features of trauma may potentiate the effectiveness of glucocorticoids and their proposed memory-disrupting properties (al Abed et al., 2020; Huff et al., 2011). Likewise, it should be further explored how exogenous glucocorticoids modulate the contextual processing impairments seen in PTSD patients (Garfinkel et al., 2014).

3.2.1. Neuroimaging effects of glucocorticoid administration

In addition to evaluating the therapeutic profile of glucocorticoid administration in PTSD patients, considerable efforts have been made to identify the precise brain areas and networks related to the effect of glucocorticoid administration on PTSD patients. To the best of our knowledge, only five studies have evaluated the neuroimaging underpinnings of glucocorticoid administration (versus placebo) in patients with PTSD and trauma-exposed healthy participants. Thus, a noticeable study explored resting-state brain metabolism in response to a parenteral hydrocortisone administration (17.5 mg) using 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET) in men with and without combat-related PTSD. Hydrocortisone administration appeared to eliminate group differences in the hemispheric laterality of the hippocampus and the ventral amygdala. Specifically, hydrocortisone increased the relative metabolic rate in the right hippocampus of the PTSD group and the left ventral amygdala in the non-PTSD group. In addition, hydrocortisone restored the inverse relationship between the anterior cingulate cortex and amygdala in PTSD individuals (Yehuda et al., 2009). Another study with a similar methodology and a parenteral administration of hydrocortisone (17.5 mg) to male combat veterans with and without combat-related PTSD found that hydrocortisone increased the hippocampal metabolic activity in the PTSD group and decreased it in the non-PTSD group, especially in the right hippocampus (Yehuda et al., 2010).

Moreover, the effects of an oral hydrocortisone administration (10 mg) on blood oxygenation level-dependent (BOLD) signal during an autobiographical memory retrieval task (AMT) inside a functional magnetic resonance imaging (fMRI) scanner in healthy participants and patients with PTSD was investigated in women. Whole-brain activity patterns during AMT did not differ between conditions or groups (neither in the placebo condition nor after hydrocortisone administration). Notwithstanding, they found that childhood trauma may be related to brain activity responsiveness to hydrocortisone. In this sense, Childhood Trauma Questionnaire scores were positively associated with hydrocortisone-induced activation of the anterior medial prefrontal cortex, ventrolateral prefrontal cortex, posterior cingulate cortex, angular gyrus, and cerebellum during AMT (Metz et al., 2019b). The same research team also used resting-state fMRI to assess hippocampal and amygdalar functional connectivity. However, these analyses did not reveal hydrocortisone-induced hippocampal or amygdalar functional connectivity changes (Metz et al., 2019b). Besides, cerebral perfusion was evaluated in the context of script-driven trauma imagery during an

Table 2
Selected characteristics of curative studies using glucocorticoids for PTSD. All studies were randomized, two-arms, double-blind and placebo-controlled, except for Ludäscher et al., 2015 and Aerni et al. (2004) with a crossover design. Wood et al. (2015) had 3 arms. BDI= Beck Depression Inventory, C = control, CAPS= Clinician-Administered PTSD Scale, d = day, EMG = electromyography, IES-R = Impact of Event Scale-Revised, IV = intravenous, MINI = Mini-International Neuropsychiatric Interview, mo = month, MR = memory reactivation, n.s. = not specified, NMR = no memory reactivation, PCL= PTSD CheckList, PDS= Posttraumatic Diagnostic Scale, PDS= Posttraumatic Stress Diagnostic Scale, PE= Prolonged exposure therapy, PO = oral, PSS-SR= PTSD Scale-Self Report, QIDS-SR = Quick Inventory of Depressive Symptomatology, SCL-90R = Symptom Checklist 90-Revised, SD = single dose, SD = single dose, TX = treatment, w = week.

ID		Demographics				Drugs			Assessments		Outcomes	
First Author	Year	Age	Gender (men/ total)	part per arm (placebo, TX)	Trauma type (type of patient)	Intention	Medication (route)	Dosage	Time points of outcome assessment	Instruments	Outcomes	Other outcomes
Suris	2010	n.s.	only men	10, 9	Combat-related military trauma (PTSD)	Curative after MR	Hydrocortisone (IV)	SD (4 mg/kg)	0, 1 w, 1 mo	CAPS, IES-R. QIDS-SR	No overall differences in PTSD symptoms. At 1 w lower avoidance/ numbing in hydrocortisone but not maintained at 1 mo.	No differences in physiological measures (heart rate, skin conductance response, corrugator, and frontalis EMG)
Ludäscher	2015	30.7 (19–44)	only women	15	Childhood sexual abuse, sexual and physical abuse (PTSD)	Curative	Hydrocortisone (PO)	7 d (placebo) + 7 d (10 mg) + 7 d (placebo) + 7 d (30 mg)	x3/d intrusions. 1/w PTSD intensity	IES-R. IES-R intrusions. SCL-90R	No differences	
Aerni	2004	40–55	2/3	3	Terrorist attack, assault, traumatic injury (PTSD)	Curative during habitual TX	Hydrocortisone (PO)	1 mo (10 mg/ d)	self > daily, clinical administered > monthly. 3 mo	CAPS self-administered. Clinical interview	Variable results, lower intensity, and frequency of reexperiencing/ physiological distress symptoms	
Yehuda	2015	C 44.2 (14.5), TX 54.9 (12.7)	only men	5, 11	Combat-related military trauma (PTSD >50 CAPS)	Curative PE augmentation	Hydrocortisone (PO)	7 times (30 mg)	0, post-tx, 6 w	CAPS. PSS-SR. BDI	Lower PTSD symptoms in hydrocortisone group. Subgroup: Greater improvements in people with greater lifetime PTSD severity	Responders to hydrocortisone had the highest pre-treatment glucocorticoid sensitivity that diminished over the course of treatment
Lehrner	2021	C 34.6 (7.68), TX 36.0 (8.07)	C 27/30, TX 27/30	30, 30	Combat-related military trauma (PTSD >60 CAPS, excl. mod-severe TBI)	Curative PE augmentation	Hydrocortisone (PO)	8 times (30 mg)	0, 1 w and 3 mo	CAPS self-administered. MINI. PDS. BDI	No effects of hydrocortisone. Subgroup: patients with current post concussive symptoms and hydrocortisone had lower hyperarousal symptoms	Patients with higher baseline glucocorticoid sensitivity had a greater reduction of avoidance symptoms with hydrocortisone
Wood	2015	C 40.5 (11.7), TX + MR 44.7 (10.4), TX + NMR 46.8 (14.5)	C 13/15, TX + MR 10/15, TX + NR 10/13	15, 15, 13	Heterogeneous (PTSD)	Curative before MR	Mifepristone (PO)	1 time (1800 mg)	0 and 1 w	IES-R. CAPS	No differences	No differences in physiological measures (heart rate, skin conductance response, corrugator and frontalis EMG)
Golier	2012	48.8 (26–63)	only men	4, 4	Combat-related military trauma (PTSD)	Curative	Mifepristone (PO)	7 d (600 mg/ d)	1 mo	CAPS. PCL	Lower PTSD symptoms in mifepristone. PTSD rate 1/4 mifepristone vs 3/4 placebo	

arterial spin labeling fMRI acquisition after an oral hydrocortisone administration (20 mg) in participants exposed to earthquake-related trauma with and without PTSD. Regional blood flow during the trauma script presentation did not show any significant effects on condition, group, or condition by group (de Kloet et al., 2016; Douglas et al., 2019).

Overall, current research appears to underline the role of the hippocampus, amygdala, and prefrontal cortex, which are characterized by a high density of corticosteroid receptors (de Kloet et al., 2016), in the neurobiological mechanism of action of hydrocortisone in patients with PTSD. However, the use of four different neuroimaging methodologies (resting-state PET, task-based BOLD fMRI, resting-state BOLD fMRI, and task-based ASL fMRI) and small sample sizes do not allow to arrive at robust conclusions, and they should be considered only preliminary. Indeed, one of the possible reasons for the negative findings observed in three of the published studies (Douglas et al., 2019; Metz et al., 2019a, 2019b) is the lack of statistical power derived from assessing small sample sizes. Moreover, the actions of glucocorticoids are conditional and time-dependent, a fact that should be also considered in further studies.

In addition, the effects of hydrocortisone may vary as a function of dose and route of administration. In this sense, single relatively low oral doses of 10–20 mg may lead to not enough intense effects to display significant neuroimaging findings. Clinical trials have used a 40 mg therapeutic dosage of hydrocortisone during a course of a few days of treatment (Yehuda et al., 2010; 2009). Interestingly, the two studies reporting a significant direct impact of hydrocortisone on brain metabolism used an intravenous injection, which may be an easier route to cross the blood-brain barrier compared to oral administration. Moreover, these were the only studies focusing their analyses on men, therefore, a sex-specific effect of hydrocortisone cannot be discarded (Yehuda et al., 2010; 2009). Although current literature arises relevant and interesting questions, further research is warranted to ascertain the neuroimaging underpinnings of glucocorticoid administration in patients with PTSD.

4. Preventive role of glucocorticoids in animal models of PTSD

As beforementioned, clinical research highlights the role of glucocorticoid administration in preventing the development of PTSD after exposure to an acute and intense stressor. Following this line, various researchers have carried out preclinical studies to delve into the mechanisms underlying the preventive role of glucocorticoids in the negative consequences of stress.

4.1. Preventive corticosterone modulation of behavioral and cognitive function

To evaluate the efficacy of glucocorticoid administration in preventing both the behavioral and the neurobiological consequences of trauma most of the research has employed PTSD-like animal models. To reproduce some of the critical neurobiological features of PTSD, current models focus on exposing animals to different types of stressors (Daskalakis et al., 2013b). Among them, inescapable foot shocks, exposure to a predator's scent (for instance, cat's or fox's urine) or single prolonged stress such as immobilization on board are the ones that show better apparent validity, since these models can reproduce emotional alterations such as high anxiety, depressive-like behaviors or impairment in fear memory (Richter-Levin et al., 2019). Indeed, all these models have also in common an overactivation of the HPA axis and a long-term impairment of emotional responses that are sensitive to the administration of antidepressants or benzodiazepines palliating the deleterious effects of stress (Bentefour et al., 2015; Smith et al., 2011).

Accordingly, the possible effect of glucocorticoid administration protecting against the deleterious effect of trauma has been explored using predator scent models. Exposure to a predator scent model modulates important traits of PTSD in rodents. However, rats repeatedly exposed to cat litter present heterogeneous anxiety and avoidance responses. Indeed, rats might be classified as low, moderate, or extreme responders depending on their scores in the elevated plus maze (EPM) and the amplitude of startle response (ASR) tests. An example of this type of research is carried out by Cohen et al. (2006), in which they compared anxiety and fear responses in different rat strains exposed to a predator odor with or without prior corticosterone treatment. This study aims at establishing the role of genetically predetermined corticosterone response to stress in the prevalence of PTSD, and then to study the involvement of corticosterone administration in highly affected rats as shown by extreme responses in the EPM and ASR tests. Interestingly, administration of corticosterone 1 h before predator odor exposure decreases the prevalence of extreme behavioral responders from 50% to 8%, showing a preventive role of corticosterone in a highly prevalent strain of rats that show posttraumatic stress responses (Cohen et al., 2006). The authors of this study suggest that activation of the HPA axis just before traumatic stress might help the HPA axis produce an effective reaction to subsequent stress and thus prevent the development of PTSD-related symptoms. Interestingly, a follow-up study by Cohen et al. (2008) demonstrates that administering corticosterone right after predator scent exposure reduces the anxiogenic consequences of traumatic stress 31 days after stress exposure (Cohen et al., 2008). These results suggest that the administration of corticosterone, nearly before or after trauma exposure, confers some type of resilience against the long-term consequences of severe stress.

Another widely used model to induce a PTSD-like phenotype in rodents is immobilization stress since it has been shown to trigger several neurobiological alterations in rodents (Andero et al., 2011; Velasco et al., 2022; Wingo et al., 2018). Using immobilization as a traumatic stress model, the administration of corticosterone at any time from 12 h before stress to 24 h after stress, has been shown to prevent the anxiety-like behavior induced by immobilization stress (Chakraborty et al., 2020; Rao et al., 2012). Even more, the anxiolytic effect of post-stress corticosterone is also accompanied by a prevention of the impairment in social interaction, and a significant reduction of circulating corticosterone 12 h after the treatment (Chakraborty et al., 2020). Further studies in mice prove that a single administration of a high dose of corticosterone 1 h after acute and severe stress protects mice against the anxiogenic and depressive effects of immobilization. These effects are accompanied by the restoration of the protein phosphatase 1F (PPM1F) expression in the medial prefrontal cortex and the amygdala (Wingo et al., 2018).

Corticosterone administration has also been tested in other models of PTSD. For instance, the administration of hydrocortisone 1 h after exploding a thin copper wire which produces multi-sensorial stress in rats, prevents the PTSD-like phenotype as measured by enhanced performance in an EPM, but not in the ASR (Zuckerman et al., 2017). Similarly, a 3-day paradigm with restraining unescapable tail-shock stress increases the ASR, which is mitigated by a corticosterone administration from 30 min before to 30 min after the stress (Jia et al., 2015). Interestingly, insufficient bedding and nesting materials during the primary stages of development induce social interaction deficits during adolescence, accompanied by lowered circulating corticosterone and ACTH, and increased GR in the medial prefrontal cortex and the dorsal hippocampus (Perry et al., 2019). However, the administration of corticosterone 30 min before the social approach test results in effective rescue of the healthy phenotype (Perry et al., 2019), therefore suggesting that corticosterone administration during adolescence might also palliate some of the deleterious effects of early-life stress.

Aberrant fear memories are a key feature of PTSD, and fear neurocircuitry is closely related between humans and rodents (Andero et al., 2013; Mahan and Ressler, 2012). Corticosterone administration affects fear memory in a dose-dependent manner since its administration after predator stress prevents the increased freezing during the retrieval phase of contextual fear conditioning (Cohen et al., 2008). However,

corticosterone does not affect cued-fear retrieval 48 or 96 h after its administration, although fear renewal is decreased (Wang et al., 2014). Notwithstanding, corticosterone administration after cued fear conditioning also suppresses fear-potentiated anxiety as measured by the EPM 1-week after the administration (Wang et al., 2014). The data reported on glucocorticoid treatment after stress highlights a preventive role of this intervention on enhanced retrieval of contextual, but not cued fear conditioning, suggesting an important role of the hippocampus and contextual learning and memory in the attenuated fear retrieval of corticosterone-treated animals. Interestingly, the disruption of contextual fear memory consolidation is hypothesized to mediate the corticosterone-induced resilience towards subsequent stressors (Cohen et al., 2008). Moreover, administration of corticosterone 1 h before exposure to cat litter does not affect learning, extinction, or reversal learning in the Morris water maze, suggesting that spatial memory remains unaltered after the corticosterone treatment (Cohen et al., 2006). Furthermore, corticosterone administration after the familiarization phase of the object recognition task impairs memory retrieval only at a high dose. Interestingly, predator scent stress exposure increases locomotor activity, and this increase was significantly higher in rats that receive corticosterone compared with saline-treated animals (Cohen et al., 2008), pointing to possible motor alterations caused by glucocorticoids.

Blood samples revealed that reduced secretion of corticosterone in basal conditions is predictive of greater anxiety and avoidance responses, correlating with a decreased corticosterone response to following stressors (Danan et al., 2018; Cohen et al., 2006). Interestingly, mild and low responder rats do not present reduced corticosterone pulses in basal conditions nor a decreased HPA axis response toward stressors (Danan et al., 2018). Furthermore, the administration of corticosterone in the aftermath of predator odor exposure decreases the prevalence of extreme behavioral responders, showing a preventive role of corticosterone (Cohen et al., 2006, 2008). Additionally, rats showing a PTSD-like phenotype present an enhanced suppression of corticosterone after methylprednisolone administration under basal conditions, suggesting that the enhanced negative feedback of the HPA axis and its regulatory mechanisms might underlie PTSD vulnerability (Danan et al., 2021). Thus, these studies highlight that reduced HPA basal activity and/or HPA's blunted reaction to stress might confer increased vulnerability to developing PTSD-like behaviors while corticosterone administration could prevent the development of PTSD-related symptoms.

4.2. Neurobiological impact of corticosterone administration after traumatic stress exposure

Among all areas studied, the hippocampus and amygdalar complex appear to be crucial hubs for stress response modulation after trauma. Sustained glucocorticoid levels induce long-term hippocampal alterations in neural physiology and neurotransmission, and recent research highlights that experience-induced vulnerabilities may be restored through the discrete administration of compounds targeting GR or MR. Indeed, prepubertal (PND 26–29) administration of a GR antagonist, or the overexpression of MR, restores the normal phenotype by regulating glutamate and gamma-aminobutyric acid (GABA) transmission (Loi et al., 2017). Interestingly, in adults, the nuclear factor-κB (NF-κB) in the hippocampus plays a major role in the preventive effects of corticosterone administered after acute severe stress. In rats, extreme behavioral responders present an upregulation of p50 and p65 NF-κB in the hippocampus, and this expression is normalized by post-stress administration of a high dose of corticosterone, thus, showing a potential role for the hippocampal NF-κB molecular complex in mediating the long-term effects of stressful experiences (Cohen et al., 2011). Similarly, rats exposed to cat litter that receives corticosterone treatment after stress show increased expression of hippocampal brain-derived neurotrophic factor (BDNF) and decreased expression of postsynaptic density-95 (PSD-95) compared to stressed animals which have not received the treatment (Zohar et al., 2011a). Additionally, rats expressing extreme responses after traumatic stress show increased expression of the immunophilin protein FKBP5 and decreased expression of GR and MR in the ventral hippocampus and PVN; while the opposite expression pattern is observed in the dorsal hippocampus (Danan et al., 2021). Further, this study proves that the AVP, which has been associated with the sensitization of the negative feedback mechanism that regulates the HPA axis (Whitaker and Gilpin, 2015), is more expressed in the supraoptic nucleus of the hypothalamus compared to moderate and low responders and no stress-exposed rodents (Danan et al., 2021). These findings provide a tentative molecular explanation for hippocampal-HPA axis regulation disturbances in PTSD-vulnerable animals.

Further, in rodents, treatment with corticosterone after traumatic stress reverts alterations in the spinogenesis and glutamatergic transmission that are observed in the amygdala, a brain region crucial in the regulation of emotional responses after stress. Single 2 h immobilization stress increases spinal density in principal neurons of the basolateral amygdala (BLA) 10 days after stress, correlating with an increase in anxiety-like behavior. Corticosterone administration in drinking water before stress prevents this increase in spinal density, especially in the proximal region of the dendrite (Rao et al., 2012). Furthermore, corticosterone administration in drinking water 24 h after stress also prevents the increase in spinal density in primary apical dendrites of BLA principal neurons, accompanied by a lower anxiety-like behavior (Chakraborty et al., 2020). In line with these results, a metaplasticity study in vitro showed that one pulse of corticosterone induces a long-lasting enhanced glutamatergic transmission in BLA neurons, while previous immobilization stress exposure or a single corticosterone pulse prevents this enhanced glutamatergic transmission (Karst et al., 2010). Repeated corticosterone-induced activation of BLA principal neurons prevents the glutamatergic-induced synaptic plasticity that accompanies the stress-induced anxiety-like behavior in rodents (Chattarji et al., 2015). The combined findings in the beforementioned data suggest that, rather than the dose, the timing of corticosterone administration is a key factor preventing stress-induced plasticity in principal neurons of the BLA.

Altogether, these data suggest that the presence of elevated levels of CORT at the time of acute stress confers protection against the detrimental behaviors induced by PTSD-like animal models, through the prevention of neuronal plasticity abnormalities in critical stress-regulation areas in the brain such as the dorsal hippocampus and the BLA.

5. Future directions

The pathophysiology underlying HPA axis alterations in PTSD patients is not well understood, but current research points to a gradual sensitization to glucocorticoid feedback leading to hypocortisolemia in a vulnerable population after stress (Schumacher et al., 2019). Therefore, traumatic experiences that involve an over-physiologic adrenergic response, coupled with a blunted cortisol response to stressful experiences, might result in a stronger encoding of traumatic memories and subjective feelings of distress. These alterations in synaptic plasticity across stress-regulator regions in the brain may eventually trigger a complex phenotype characterized by alterations in perception and thoughts (Yehuda, 2002).

Pharmacological glucocorticoid-based interventions occurring shortly after a traumatic event may be the most effective approach to disrupt fear memories, by halting their consolidation, in what some authors have called the "golden hours", namely a defined and limited temporal window when the response triggered by trauma could be modified (McGaugh, 2000; Zohar et al., 2011a). However, this theoretical approach may be useful for individuals with hypocortisolemic responses toward stress but may not apply to all individuals, as glucocorticoids could even enhance the consolidation of fear-motivated

behaviors in individuals who do not have a blunted HPA response. Research has identified plenty of risk factors for PTSD, although individual risk prediction remains elusive due to the lack of clinical studies and the heterogeneity of their nature. Current models and analyses of PTSD risk disregard interindividual differences, and they oftentimes homogenize groups of patients suffering from PTSD after several types of traumatic experiences, that differ in intensity, duration, and nature of the stressors (e.g., motor vehicle accidents, war combat, sexual abuse) (Qi et al., 2016). Analyses focused on individual symptom trajectories and the use of algorithms may help to make better treatment predictions in patients at identified risk of PTSD after a stressful experience (Galatzer-Levy et al., 2014; Schultebraucks et al., 2020). Indeed, these studies appear to be crucial to identifying the specific traits that make a population more likely to positively respond to glucocorticoid-based therapies.

Although evidence for a beneficial effect of glucocorticoids for PTSD prevention or decreased severity of PTSD symptoms has been reported (onset and symptom intensity), the quality of the evidence is moderate, with most of the studies having a considerable risk of bias and relying on small samples. Still, it is unknown whether universal prevention of PTSD with hydrocortisone is feasible given the adverse effects profile of the drug, the constrained dosing during the "golden hours" and the patients' agreement (Astill Wright et al., 2019). It is still necessary to frame the limitations of this intervention since some studies have found that glucocorticoid-based administration has only been beneficial for a subset of patients (Delahanty et al., 2013; Kok et al., 2016; Shaked et al., 2021). Of note, the studies reported on glucocorticoid-based pharmacotherapy for the treatment of PTSD remain controversial. Future studies that include larger sample sizes, homogeneous methods, and consider individual data and symptom trajectories may be able to arrive at stronger conclusions.

Similar to all pharmacological interventions, the use of glucocorticoids should be weighed against their risks since sustained glucocorticoid use carries possible side effects like insomnia, edema, hypomania, electrolyte imbalances, or suppression of the HPA axis (Warrington and Bostwick, 2006; Williams, 2018). Although the adverse effects profile is not reported in many of the studies, this might be related to the higher dropouts in treatment groups. Moreover, only one of the reported studies found that hydrocortisone administration shortly after trauma was detrimental to clinical and psychiatric outcomes in a subset of people at risk of suffering from PTSD (Shaked et al., 2021). Thus, in general, it seems that glucocorticoid administration shows a safety profile, although the possible side effects must be carefully considered in the design of future studies and clinical approaches.

Preclinical studies have emerged as a plausible tool to further investigate the underpinnings of glucocorticoid-based prevention of PTSD after traumatic stress due to its high translational value and precise interventions. These studies have shown that glucocorticoid administration either preceding or immediately following a traumatic stressor, confers protection against the development of PTSD emotional and cognitive symptoms and mitigates the impact of stress on brain areas such as the hippocampus and amygdala. Although most of the available research has been focused on the regulative role of glucocorticoid administration on the hippocampus after stress, further research should address the precise mechanisms of their anxiety-related profile in the amygdala. Some discrepancies might be found between human and animal studies; however, the use of animal models appears to be decisive to understand the molecular and systemic mechanisms underlying the preventive effect of glucocorticoid administration after stress. Some of these advantages are considering sex and age as biological variables, the precise control of dosages and administration windows, and the development of even more precise models to identify a vulnerable phenotype. Regarding interindividual differences, it is especially noticeable that most studies addressing glucocorticoids as preventive agents report exclusively data on male subjects. Most evidence has shown differences in the functioning of the HPA axis and memory formation between male and female animals and humans. Indeed, PTSD is twice as prevalent in women than in men (Bangasser and Valentino, 2014). Thus, it must be taken into consideration of the possible sex differences in vulnerability and response to the treatment for future studies.

Overall, the existing studies that evaluate the efficacy of glucocorticoid-based therapy for preventing PTSD are encouraging. Notwithstanding, the specific mechanisms that mediate this effect and the population that might benefit from it remain elusive for research, due to methodological differences and gaps in translational studies. Further studies are warranted to explore the effectiveness of this intervention, the specific populations of interest for this treatment based on individual differences, and to identify the neurobiological mechanisms underpinning its efficacy.

Declarations of competing interest

None.

Data availability

No data was used for the research described in the article.

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