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Pharmacological Modulation of Acute Trauma Memories to Prevent PTSD: Considerations from a Developmental Perspective

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Abstract

Estimates of the lifetime prevalence of posttraumatic stress disorder (PTSD) in American adults range from 6.4–6.8%. PTSD is associated with increased risk for comorbid major depression, substance use disorder, suicide, and a variety of other mental and physical health conditions. Given the negative sequelae of trauma/PTSD, research has focused on identifying

efficacious interventions that could be administered soon after a traumatic event to prevent or reduce the subsequent incidence of PTSD. While early psychosocial interventions have been shown to be relatively ineffective, early (secondary) pharmacological interventions have shown promise. These pharmacological approaches are largely based on the hypothesis that disruption of altered stress hormone levels and the consequent formation of trauma memories could protect against the development of PTSD. The present manuscript reviews the literature regarding the role of peri-traumatic stress hormones as risk factors for the development of PTSD and reviews evidence for the efficacy of exogenously modulating stress hormone levels to prevent/buffer the development of PTSD symptoms. Whereas prior literature has focused primarily on either child or adult studies, the present review incorporates both child and adult studies in a developmental approach to understanding risk for PTSD and how pharmacological modulation of acute memories may buffer the development of PTSD symptoms.

Keywords

Posttraumatic stress disorder; propranolol; hydrocortisone; developmental; cortisol; trauma memories

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Over the past decade, advances in our understanding of the biology of posttraumatic stress disorder (PTSD) have supported the examination of pharmacological approaches initiated soon after trauma exposure in order to reduce or eliminate the development of PTSD in recently traumatized individuals. These so-called secondary intervention approaches have largely been conceptualized and designed from the premise that modulation of stress hormones and the consequent formation of trauma memories could protect against the development of PTSD symptoms. However, inconsistencies abound in these literatures, with perhaps the largest concerning observed differences in findings of studies examining child versus adult trauma victims, necessitating the conceptualization of traumatic stress and early intervention approaches from a developmental perspective. Prior to reviewing the evidence for the initial efficacy and promise of early pharmacologic interventions to prevent/buffer the development of PTSD, the present review will provide a brief historical overview of the role of stress hormones in emotional memory formation with a focus on how altered stress hormone levels can result in aberrant memory formation/PTSD in adults and children. We will then review findings of studies testing early secondary pharmacologic approaches and conclude with a discussion of limitations and important moderators/confounds that need to be considered in future research.

The Role of Stress Hormones in Emotional Memory Formation

Emotionally arousing events are more likely to be remembered than trivial events due to the facilitating influence of stress hormones (McGaugh, 2003). Emotional arousal and the accompanying release of stress hormones from the sympathetic nervous system (SNS) (i.e., epinephrine and norepinephrine) and the hypothalamic pituitary adrenal (HPA) axis (i.e., glucocorticoids) appear to be important factors in the consolidation and retention of memories for emotionally arousing events.

The Role of the SNS in Emotional Memory

Following stressor onset, the SNS responds with the rapid release of epinephrine and norepinephrine (Sapolsky, Romero, & Munck, 2000). Both human and animal studies have demonstrated that initial SNS activation enhances memory via a number of secondary messenger systems in the basolateral amygdala, while pharmacologically blocking SNS activity inhibits this enhanced memory formation (for reviews see McGaugh, 2000; McGaugh, McIntyre, & Power, 2002). Collectively, this research underscores the influential role of epinephrine and norepinephrine in the consolidation and retention of memories for emotional events.

The Role of the HPA Axis in Emotional Memory

Glucocorticoids – the end product of HPA axis activation – are released in conjunction with epinephrine/norepinephrine but reach peak levels more slowly after stressor onset. Glucocorticoids exert a number of cardiovascular, metabolic, immune, and neurobiological effects that serve to rally resources to confront challenge (Sapolsky et al., 2000). In addition, increases in glucocorticoid levels also serve to contain acute SNS stress responses (Joëls, Fernandez, & Roozendaal, 2009; Ursin & Olff, 1993). Although consistently linked to memory regulation, early research produced conflicting findings regarding whether

glucocorticoids facilitated or impaired memory for emotional events. Initial animal research suggested that, if administered in close proximity to the time of learning, exogenous glucocorticoids could enhance memory (e.g., Flood et al., 1978; Kovacs, Telegdy, Lissak, 1977). However, other research demonstrated a deleterious effect of glucocorticoids on memory retrieval when glucocorticoids reached peak concentrations after initial learning (Buchanan, Tranel, & Adolphs, 2006; de Quervain, Roozendaal, & McGaugh, 1998; Kuhlman, Piel, & Wolf, 2005). These findings and others demonstrating that glucocorticoid administration after initial learning impairs memory retrieval and declarative memory performance (Lupien & McEwen, 1997; Newcomer et al., 1999; Wolkowitz et al., 1990) raise the possibility that therapeutic disruption of retrieval mechanisms soon after a traumatic event might protect against the development of PTSD symptoms by disrupting the cycle of retrieving, re-experiencing, and reconsolidation that has been hypothesized to lead to PTSD (de Quervain, Aerni, Schelling, & Roozendaal, 2009).

More recent research has suggested that the effect of glucocorticoids on memory is time-dependent. More specifically, during stressor exposure, rapid non-genomic glucocorticoid actions in the basolateral amygdala appear to facilitate the enhancing effects of epinephrine and norepinephrine on memory formation (for review see Groeneweg, Karst, de Kloet, & Joëls, 2011). In contrast, slower genomic glucocorticoid actions take effect an hour or more after stressor exposure and suppress the processing of new information (Joëls, Pu, Wiegert, Oitzl, & Krugers, 2006). These genomic actions have two effects: 1) they promote the consolidation – and subsequent retrieval – of memories for information encountered *during* the stressor by reducing competing information encountered *after* the stressor's termination and by extension 2) they prevent the formation – and subsequent retrieval – of memories for information encountered *after* initial glucocorticoid release (see Figure 1 part A which was adapted and expanded upon from Schwabe, Joëls, Roozendaal, Wolf, & Oitzl, 2012). Thus, initial non-genomic effects serve to facilitate memory formation, while delayed genomic effects serve to shut down acute stress responses, promote the consolidation of information learned near the time of the stressor, and inhibit the formation and subsequent retrieval of information encountered after the stressor has been experienced. When peri-traumatic levels of cortisol are altered, these processes can be affected, and may result in overconsolidation and impaired memory retrieval.

Adult Studies Examining Stress Hormones in PTSD

Stress Hormone Correlates of Chronic PTSD

Given the essential role of stress hormones in memory formation and the fact that PTSD is a possible outcome of a traumatically stressful event, early research into biological markers/ correlates of PTSD largely focused on determining whether individuals with PTSD differed from controls on levels of SNS and HPA axis stress hormones. These studies found that chronic PTSD patients had greater 24-hour urinary epinephrine/norepinephrine excretion and higher norepinephrine reactivity to psychological stress than controls (Friedman, 1991; Kosten et al., 1987; Strawn & Geraciotti, 2008; Yehuda et al., 1992), suggesting a persistent elevation of SNS hormones in PTSD. Paradoxically, early studies revealed lower levels of cortisol (the principle glucocorticoid in humans) in individuals with PTSD versus trauma-

exposed and non-exposed controls (Friedman, 1991; Mason, Giller, Kosten, Ostroff, & Harkness, 1986; Yehuda, Boissoneau, Lowy, & Giller, 1995; Yehuda et al., 1990). However, subsequent research produced results counter to these with some studies finding significantly higher levels of cortisol in people with PTSD versus controls (for review see Rasmusson, Vythilingam, & Morgan, 2003). Failure to account for a number of factors known to impact HPA axis functioning (e.g., age, gender, medication status, cigarette smoking status, etc.) (Nicolson, 2008) has been hypothesized as a possible reason underlying these equivocal findings (Rasmusson et al., 2003). Further, more recent research assessing cortisol levels in hair samples suggests that the relationship between PTSD symptom severity and hair cortisol levels in adults depends upon the length of time since trauma exposure. Hair sampling averages cortisol across a much longer window of time (1 month for every 1 cm of hair analyzed) than urine or saliva sampling, reducing the impact of the many confounds that can influence cortisol levels. Although initial hair cortisol research suggested that PTSD was associated with higher hair cortisol levels in adults experiencing ongoing trauma (Steudte et al., 2011), Steudte et al. (2013) found that lower hair cortisol levels were associated with a greater length of time since trauma exposure as well as with higher PTSD intrusion symptoms.

Early Stress Hormone Predictors of PTSD

Based upon the findings of altered stress hormone levels in chronic PTSD, researchers hypothesized that abnormalities observed in chronic PTSD patients, if present during and soon after trauma, could be associated with abnormal memory formation and increased risk for developing PTSD. Pitman (1989) was the first to hypothesize that heightened sympathetic activity at the time of the traumatic event could lead to the development of 'overconsolidated' trauma memories, and result in the intrusive memories characteristic of PTSD. Subsequent trauma reminders were hypothesized to serve as cues that activated trauma memories leading to additional sympathetic hormone release and the further strengthening of these memories. Yehuda and Harvey (1997) expanded this theory to include the at-that-time, relatively consistent findings of low cortisol in chronic PTSD. More specifically, they suggested that during and soon after traumatic stress, exaggerated catecholamine increases without accompanying cortisol increases could lead to inappropriate memory consolidation (either over-salient or fragmented memories) and subsequent symptoms of PTSD (Yehuda & Harvey, 1997; Yehuda, McFarlane, & Shalev, 1998). Based on these hypotheses, researchers began assessing stress hormones soon after trauma in an attempt to identify reliable biological risk factors for PTSD.

SNS—Early studies designed to identify biological risk factors for PTSD that were present soon after trauma exposure focused on patients acutely hospitalized for traumatic injury. Although contradictory findings have been reported in a study of self-selected participants (Blanchard, Hickling, Galovski, & Veazey, 2002) and results may not generalize to seriously injured trauma patients (Buckley et al., 2004), prospective studies of consecutive emergency department patients found that people with higher heart rates during their hospital stay were more likely to develop PTSD or PTSD symptoms (Bryant, Harvey, Guthrie, & Moulds, 2000; Shalev et al., 1998; Zatzick et al., 2005) suggesting that elevated SNS activity near the time of trauma may be a risk factor for subsequent trauma symptoms.

HPA axis—Studies examining cortisol levels in adults soon after trauma have generally found that lower cortisol is associated with increased risk for developing PTSD symptoms. Female rape victims with lower serum cortisol levels during a post-sexual assault medical exam had more PTSD symptoms at 6-week follow-up than victims with higher cortisol levels (Walsh et al., 2013). Research using 15-hour urine samples with collection initiated upon hospital admission found that victims who met acute PTSD diagnostic criteria 6-weeks after an MVA had significantly lower urinary cortisol levels in the immediate aftermath of the accident than victims who did not meet diagnostic criteria (Delahanty, Raimonde, & Spoonster, 2000). In addition, in-hospital levels of cortisol were negatively correlated with subsequent intrusive and avoidant symptoms of PTSD ($r = -0.46, p < 0.01$). Lower in-hospital salivary cortisol levels were also found to predict the subsequent development of PTSD symptoms in another sample of MVA victims (Ehring, Ehlers, Cleare, & Glucksman, 2008). However, a larger study of individuals admitted to a hospital emergency room found that those who subsequently did and did not develop PTSD did not differ on in-hospital plasma, salivary, or urinary cortisol, or plasma and urinary norepinephrine levels (Shalev et al., 2008; Videlock et al., 2008), leading the researchers to hypothesize that the complex etiology of PTSD could not be described with simple biological risk models. Despite these negative findings, recent reviews of the adult literature have concluded that individuals vulnerable for the development of PTSD display dysregulated glucocorticoid functioning at various points along the glucocorticoid signaling cascade, including lower levels of circulating cortisol soon after trauma exposure (van Zuiden et al., 2013).

Child Studies Examining Stress Hormones in PTSD

The child traumatic stress literature developed in parallel to studies conducted in adults, with initial studies examining differences in children with chronic PTSD and subsequent studies extending these findings to studies of early biological predictors of PTSD symptoms.

Stress Hormone Correlates of Chronic PTSD

Consistent with the adult literature, chronic PTSD in children appears to be characterized by elevated levels of sympathetic arousal (De Bellis et al., 1999; Perry, 1994) and mixed findings regarding the direction of HPA axis alterations. De Bellis et al. (1999) found that children with PTSD (stemming from traumas occurring, on average, 2 years prior) had higher urinary cortisol levels than controls, and that cortisol levels were positively correlated with duration of trauma and PTSD symptom severity. In contrast, other studies found lower cortisol levels in children with chronic PTSD (Goenjian, Yehuda, Pynoos, Steinberg, & et al, 1996; King, Mandansky, King, Fletcher, & Brewer, 2001). However, these studies differed greatly with respect to the manner in which PTSD symptoms/diagnosis were assessed, the length of time since trauma, the age range and gender ratio of children assessed, the manner in which cortisol was assessed (urine versus saliva), and the timing of physiological assessments. Accordingly, contradictory findings may have been due to these methodological differences across studies.

Early Stress Hormone Predictors of PTSD

SNS—Few studies have explored acute biological predictors of PTSD in children.

Consistent with the adult literature, elevated heart rate soon after trauma has been associated with increased risk for the development of PTSD in child trauma victims (De Young, Kenardy, & Spence, 2007; Kassam-Adams, Garcia-España, Fein, & Winston, 2005; Nugent, Christopher, & Delahanty, 2006). This is consistent with experimental research finding that heart rate reactivity to a mild stressor enhances children's memory for events occurring near the time of the stressor (Quas, Bauer, & Boyce, 2004; Quas & Lench, 2007).

HPA axis—In contrast with the results of adult research, in traumatized children, *higher* cortisol levels in the acute aftermath of the trauma have been shown to predict subsequent PTSD symptoms and diagnosis (Delahanty, Nugent, Christopher, & Walsh, 2005; Kolaitis et al., 2011; Ostrowski et al., 2007). It should be noted that, in two of these studies (Delahanty et al., 2005; Ostrowski et al., 2007), the positive correlations between cortisol levels and PTSD were driven by significant findings in boys (all $r_s \geq 0.50$) that were not present in girls.

Developmental models have attempted to account for the differing findings regarding the direction of cortisol abnormalities in at-risk children and adults (De Bellis 2001; Delahanty and Irish, 2008). According to De Bellis's developmental traumatology model, at-risk child trauma victims may respond to a traumatic event with abnormally elevated HPA axis activity and heightened cortisol release. Hypersecretion of cortisol may then interfere with normal HPA axis functioning resulting in an enhanced negative feedback loop. Over time, likely years, the enhanced negative feedback loop would result in lower basal and reactive cortisol levels, as sometimes observed in adult trauma victims. This theory also accounts for initially contradictory findings in child trauma studies: research examining children within two years post-trauma tends to find a positive relationship between cortisol levels and PTSD symptoms (De Bellis, Lefter, Trickett, & Putnam, 1994; De Bellis, et al., 1999; Delahanty et al., 2005), while five years post-trauma lower levels of cortisol in child victims are associated with PTSD symptoms (Goenjian et al., 1996). Furthermore, Weems and Carrion (2007) found that, in children with PTSD stemming from a trauma occurring within the last year, a positive relationship existed between PTSD symptoms and cortisol levels. However, a negative relationship between PTSD symptoms and cortisol levels was observed for children with PTSD from a trauma occurring more than a year prior (although this relationship did not reach statistical significance). These findings highlight the importance of taking into account the recency of trauma exposure when examining the relationship between cortisol and PTSD.

Still stronger evidence for the impact of time since trauma exposure on the relationship between cortisol and PTSD comes from a recent meta-analysis of adult and child studies examining HPA axis functioning in PTSD. Results of this meta-analysis indicated that, on average, as the length of time since the focal trauma increases, daily cortisol output decreases (Morris, Compas, & Garber, 2012). These findings underscore the importance of considering biological findings in PTSD from a lifespan standpoint and highlight the

potential role of prior childhood trauma in altering physiological reactivity to a subsequent trauma and increasing risk for PTSD.

Pharmacological Treatments

Treatments Impacting SNS Arousal

Given consistent findings of heightened SNS activity associated with increased risk for PTSD in both child and adult trauma victims, secondary pharmacological interventions initially targeted early post-trauma sympathetic arousal. These studies followed from suggestive trials of SNS receptor antagonists in chronic PTSD. A number of open-label trials have suggested the efficacy of the alpha receptor antagonist Prazosin at reducing psychological distress and trauma-related sleep disturbances in people with chronic PTSD due to combat or civilian trauma (Peskind, Bonner, Hoff, & Raskind, 2003; Taylor & Raskind, 2002; Taylor et al., 2006). Further, two randomized trials examining Prazosin have been conducted in adults with chronic PTSD. Both demonstrated a reduction in PTSD-related sleep disturbances and nightmares in participants receiving Prazosin; however, findings with regard to PTSD symptoms were more mixed. One trial found an improvement in global PTSD symptoms (Taylor et al., 2008), but the other found no difference in PTSD symptoms between Prazosin and placebo recipients (Raskind et al., 2007).

Considerably more research has investigated the beta receptor antagonist propranolol as a pharmacological preventative agent against the development of PTSD. Propranolol has been shown to reduce skin conductance and subjective arousal (Grillon, Cordova et al. 2004), amygdala activity (Hurlemann et al., 2010), and laboratory-based startle responses (Soeter and Kindt, 2011). Further, if administered in the acute (within hours) aftermath of trauma exposure, propranolol is thought to reduce the likelihood of developing PTSD through its influence on memory consolidation and reconsolidation (Pitman and Delahanty 2005; D'biec and LeDoux 2006; D'biec, Bush, & LeDoux, 2011). Initial pilot studies testing the efficacy of a 10-day regimen of propranolol at preventing the development of PTSD revealed that propranolol (40mg four times per day initiated within 20 hours of the trauma) recipients demonstrated less physiological reactivity to trauma cues 3-months post-trauma (Pitman et al., 2002), as well as a reduced incidence of PTSD 2-months post-trauma (Vaiva et al., 2003). However, more recent research has not been as supportive. In a randomized double-blind placebo control design with an alternate dosing strategy (20mg three times per day titrated over two days to 40mg 3 times per day), Stein and colleagues (2007) found no differences between patients receiving propranolol versus placebo at either 4- or 12-weeks post-trauma. It should be noted that the propranolol regimen for the Stein et al. (2007) study was initiated within 48-hours of trauma – a considerably longer delay until medication initiation than occurred in the Pitman et al. (2002) and Vaiva et al. (2003) studies. As propranolol's mechanism of efficacy appears to be reduction of sympathetic arousal and the decreased impact of SNS arousal on initial trauma memory formation, it appears to be critical that the initial dose occurs as soon as possible after the trauma (See Figure 1 part B).

Research examining pharmacological interventions targeting SNS activity in child trauma victims is limited. Two case studies examining the use of the noradrenergic receptor antagonist clonidine for the treatment of chronic PTSD in child physical abuse victims

suggested efficacy in reducing PTSD symptoms and trauma-related nightmares while participants were receiving the drug (Horrigan, 1996; Porter & Bell, 1999); however, once the medication was discontinued, symptoms returned. With respect to secondary prevention protocols, we are aware of only two studies in child trauma victims. In a retrospective chart review study, pediatric burn patients who had received propranolol within 30 days of hospital admission did not differ from patients who did not receive propranolol in the incidence of acute stress disorder (Sharp, Thomas, Rosenberg, Rosenberg, & Meyer III, 2010). However, as mentioned above, research has underscored the importance of initiating propranolol regimens very soon (within hours) after trauma; including individuals who received propranolol up to 30 days following trauma limits conclusions that can be drawn regarding the utility of propranolol as a secondary intervention in child trauma victims.

To date, only one randomized double-blind trial has examined the efficacy of propranolol at reducing PTSD symptoms in pediatric injury patients (Nugent et al., 2010). Results indicated no overall difference between participants who received a 10-day propranolol regimen and those who received placebo; however, in adherent participants, a treatment by gender interaction was detected. Propranolol decreased PTSD symptoms in boys while it was associated with an increase in symptoms in girls. Although the increased symptoms in female propranolol recipients could have been due to a greater proportion of bereaved girls being randomized to the propranolol condition, these results underscore the importance of examining child gender as an important moderating variable in secondary pharmacological studies.

In sum, there is preliminary evidence that pharmacologically blocking sympathetic arousal may be efficacious at reducing the development of some PTSD symptoms. Existing studies suggest that propranolol (or other SNS antagonists) should be initiated as soon as possible following the trauma, as studies administering propranolol within hours post-trauma tend to find greater efficacy at decreasing PTSD symptoms. Propranolol appears to be most efficacious at reducing the conditioned fear symptoms of PTSD, and adjunct therapy should be considered to address the other PTSD symptom clusters. Finally, although there is a dearth of studies examining propranolol as a secondary intervention in child trauma victims, the one existent study suggests caution in administering propranolol to acutely traumatized girls.

Treatments Impacting Glucocorticoid Levels

As reviewed above, basic research has implicated glucocorticoids in memory formation and recall, and dysregulated HPA axis functioning has been reported in individuals with PTSD. Therefore, manipulation of cortisol levels soon after trauma experience has also been examined as a potentially efficacious secondary intervention. Similar to studies of SNS antagonists, initial secondary cortisol trials were informed by research examining the impact of cortisol on symptoms in individuals with chronic PTSD.

Both animal and human research has found that exogenous administration of hydrocortisone modulates memory formation (Lupien & McEwen, 1997; McEwen & Sapolsky, 1995), leading researchers to consider the potential efficacy of increasing cortisol levels in people experiencing chronic PTSD in an effort to reduce distressing trauma memories. Aerni et al.

(2004) found that 10mg of hydrocortisone administered orally for 1-month resulted in a greater than 38% reduction in self-reported distress associated with traumatic memory in three chronic PTSD patients. In a larger sample of male combat veterans with chronic PTSD, Suris et al. (2010) found that 4mg/kg of hydrocortisone delivered intravenously was effective in significantly reducing the avoidance/numbing symptoms of PTSD.

Of the secondary pharmacological agents examined up to now, exogenously increasing levels of cortisol through the administration of hydrocortisone has produced the most promising results. Schelling and colleagues (2001; 2004) found that intravenous hydrocortisone delivered in-hospital was effective at reducing the incidence of subsequent PTSD in people experiencing medical trauma (i.e., septic shock and cardiac surgery). In addition, Zohar et al. (2011) examined the efficacy of a single high dose of hydrocortisone (100–140mg) at reducing the development of PTSD symptoms in 25 individuals experiencing a variety of different types of traumatic injury requiring hospitalization. Results indicated that individuals receiving hydrocortisone reported fewer PTSD symptoms 2-weeks and 3-months post-intervention compared to individuals receiving placebo. A parallel animal study found that hydrocortisone-treated animals had increased dendritic growth and spine density as well as increased levels of brain-derived neurotrophic factor, suggesting a possible mechanism through which the hydrocortisone operated. More recently, Delahanty and colleagues (2013) demonstrated that low-dose hydrocortisone administration during the acute phase of trauma responding was efficacious at reducing the incidence of PTSD symptoms in a heterogeneous trauma sample. More specifically, 64 traumatic injury patients were randomly assigned to either a 10-day regimen of low-dose hydrocortisone (20mg two times daily) or placebo. Hydrocortisone recipients reported fewer PTSD and depression symptoms 1- and 3-months later, and had greater improvements in health-related quality of life than did placebo recipients, with the largest effects observed for hydrocortisone recipients who had not received prior mental health treatment.

To date, no study has examined the potential efficacy of exogenously increasing cortisol levels in traumatized children, perhaps due to the finding that higher levels of cortisol soon after trauma have been associated with increased risk for PTSD in children (Delahanty et al., 2005; Kolaitis et al., 2011; Ostrowski et al., 2007). However, it may be premature to discount the possible efficacy of hydrocortisone treatment in child trauma victims. De Quervain and colleagues (2009) conducted a systematic review detailing how prior mixed findings can be consolidated to explain how cortisol can regulate memory formation and how dysregulation of cortisol release can be associated with PTSD. Consistent with contemporary models describing the role of stress hormones in memory formation (see Figure 1 part A), in their review they conclude that glucocorticoids interact with emotional arousal-induced increases in norepinephrine to enhance memory consolidation for traumatic events. However, this model makes different predictions for the efficacy of exogenously administered hydrocortisone soon after trauma (see Figure 1 part C). As glucocorticoids enhance consolidation of stressful memories, elevations in cortisol during the trauma could contribute to the formation of trauma memories (Schelling et al., 2004). However, following initial consolidation, sustained elevations of cortisol in the days and weeks following trauma might facilitate extinction learning by interfering with the reconsolidation and subsequent retrieval of the original trauma memory – thereby interrupting the typical cycle of retrieving,

re-experiencing, and re-consolidation of the trauma memory (de Quervain et al., 2009). Therefore, although higher levels of cortisol have been associated with subsequent increased risk for PTSD in children (particularly boys), continued elevation of cortisol levels (via exogenously administered hydrocortisone) may hold promise for facilitating extinction learning and impairing retrieval of the original trauma memory – thereby decreasing subsequent PTSD symptoms.

Although the present findings are promising regarding the use of hydrocortisone as a secondary preventive intervention for PTSD in adults, prior studies have differed in the dose and duration of medication administration. Future research can inform both dose and duration considerations as well as address feasibility questions by determining whether timing of medication initiation is critical to the efficacy of hydrocortisone. If hydrocortisone remains efficacious when medication initiation is delayed to a day or two post-trauma, it represents a more feasible early intervention agent than propranolol whose efficacy appears to be contingent upon early administration post-trauma.

Challenges to Be Met in Future Research

In addition to informing dose and duration questions and expanding upon the knowledge base of potentially efficacious early pharmacological interventions, future research into secondary interventions to prevent PTSD will need to address a number of challenges and potential confounds. Although a review of all potential confounds would be prohibitively long and well beyond the scope of the present manuscript, we focus on three critical factors that impact both biological research in PTSD and studies of the efficacy of secondary interventions: the inability to predict who is likely to develop PTSD, the importance of teasing apart developmental influences from trauma history, and the importance of considering child trauma victims as part of a family systems approach.

Perhaps the largest challenge to testing early secondary interventions is the difficulty in reliably predicting who is most likely to develop PTSD. It is difficult to demonstrate the efficacy of any early intervention if a significant percentage of participants do not develop the disorder that is meant to be intervened upon. Prior research has used a variety of ways of detecting individuals at increased risk for developing PTSD following trauma: initial heart rate levels (Pitman et al., 2002), a variety of questionnaires/screeners (Delahanty et al., 2013; Winston et al., 2003), and initial PTSD symptoms (Zohar et al., 2011). None of these screeners were particularly effective at identifying individuals who were likely to develop PTSD. Future research into determining reliable ways in which to identify trauma victims at risk for PTSD will lead to the targeting of limited intervention resources as well as allow for better testing of early secondary interventions.

As reviewed above, children and adults differ with respect to the direction of the relationship between peri-traumatic cortisol levels and subsequent PTSD symptoms and with respect to the efficacy of different pharmacological agents. These findings suggest the importance of considering the impact of trauma and efficacy of intervention approaches from a developmental standpoint. However, although these findings have been couched in terms of differences between child and adult trauma victims, currently it is impossible to tease apart

developmental differences from differences in trauma history. Previous meta-analyses have concluded that prior trauma history is consistently associated with PTSD, but to a varying extent and with somewhat low effect sizes (weighted $r < 0.30$; Brewin, Andrews, & Valentine, 2000; Ozer, Best, Lipsey, & Weiss, 2003). Possible explanations for the lower effect sizes include a failure to consider whether the prior trauma was similar or dissimilar to the index trauma (Dougall et al., 2000) or to consider different characteristics of the prior trauma (e.g., age of occurrence, stressfulness of prior trauma, extent of personal injury, etc.: Irish et al., 2008). Further, assessment of trauma history is by necessity retrospective, and stressful experiences early in development may not be consciously remembered, yet may influence responding to subsequent stressors experienced later in life. Conscious recollection of stressful experiences in the first 2–7 years of life is impaired due to an underdeveloped nervous system that lacks a mature hippocampus and neocortex as well as the mature synaptic connections between these structures (for a review see Josslyn & Frankland, 2012). At this point, it is impossible to determine whether observed differences in the biology of PTSD between children and adults reflect developmental differences or are a consequence of adult samples having been more likely to have experienced a prior traumatic event. Future research in both adults and children involving sufficiently sized subgroups of previously and non-previously traumatized individuals is necessary in order to answer this question.

Specific challenges exist in conducting research on the biology of PTSD in children. Although adults are relatively autonomous in their approach to trauma recovery, a major confound that must be addressed in child trauma studies is the influence of parental responses on a child's recovery. Parental responses to a child's trauma can impact the child's recovery following a traumatic event, and have been found to moderate early risk factors. Parental PTSD symptoms are correlated with child PTSD symptoms (for a meta-analysis see Morris, Gabert-Quillen, & Delahanty, 2012), and low parental PTSD symptoms have been found to buffer risk for PTSD in children who were at risk according to initial cortisol responses to the trauma (Nugent, Ostrowski, Christopher, & Delahanty, 2007). Parental PTSD symptoms stemming from the child's trauma have been more strongly related to the development of PTSD in children than general parental distress (Nugent et al., 2007; Pelcovitz et al., 1998), suggesting specific risk afforded by parental PTSD symptoms and underscoring the importance of examining parental PTSD symptomatology as a contributing factor to the development and persistence of PTSD symptoms in child trauma victims. Although a number of additional factors may impact findings regarding the biology of PTSD and the efficacy of early pharmacological approaches (e.g., type of trauma, presence of injury, gender, etc.) elucidation of the role of prior trauma versus developmental influences on findings, clarification of the impact of parents on a child's post-trauma recovery and improved means of identifying at-risk trauma victims soon after trauma, will greatly aid in advancing research into secondary preventive interventions for PTSD.

Conclusions

As summarized in Figure 1, increased levels of glucocorticoids during periods of sympathetic arousal are necessary to consolidate emotional memories. Aberrant levels of these hormones (as typically found in a minority of trauma victims) are associated with increased risk for the development of PTSD symptoms. In adults, low levels of cortisol have

been associated with increased risk for the development of PTSD; however, in children, cortisol and PTSD symptoms are positively related. Whereas this difference may reflect developmental differences, it may also simply reflect the impact of prior trauma history; in order to inform early intervention approaches and developmental models of PTSD, it is critical to disentangle the influence of trauma history from findings of child and adult trauma victims. Regardless, early pharmacologic interventions have been examined in both adults and children, with early propranolol administration showing promise for preventing conditioned fear-related symptoms of PTSD. Future research should examine the efficacy of early propranolol in conjunction with a tiered treatment approach to determine whether early propranolol administration decreases the need for, or aids in increasing the efficacy of, later treatment approaches (e.g., prolonged exposure, cognitive behavioral therapies, alternative medication treatments). In addition, although propranolol has been most commonly examined, alternative SNS antagonists which have shown efficacy in chronic PTSD may also show promise as secondary intervention approaches (e.g., Prazosin or Clonidine).

Although only examined in adults, a handful of studies have found that early hydrocortisone administered over differing doses and durations is efficacious at preventing PTSD symptoms. It is hypothesized that hydrocortisone facilitates extinction learning through both non-genomic and genomic effects. Future research is needed to determine appropriate dosing and timing/duration of preventive hydrocortisone therapy as well as to examine the efficacy of hydrocortisone in children and trauma victims with and without a trauma history.

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Figure 1.

A) Following stressor onset, the rapid release of norepinephrine/epinephrine combined with the rapid non-genomic effects of glucocorticoids serve to facilitate memory formation, while the slower genomic effects of glucocorticoids suppress information unrelated to the event precipitating initial glucocorticoid release; B) Following trauma exposure, excess levels of norepinephrine/epinephrine combined with non-genomic glucocorticoid effects facilitate trauma memory formation, while the slower genomic effects of glucocorticoids suppress non-trauma related information in at-risk victims, leading to the intrusive memories and reexperiencing symptoms characteristic of PTSD. The administration of sympathetic blockers (e.g., propranolol) near the time of trauma inhibits the facilitating effects of norepinephrine/epinephrine on trauma memory formation; C) glucocorticoid administration (e.g., via hydrocortisone) in the days and weeks following trauma enhances extinction learning through non-genomic glucocorticoid effects on norepinephrine/epinephrine. In addition, glucocorticoid augmentation facilitates extinction learning by suppressing the retrieval of the original trauma memory through genomic glucocorticoid effects. Figure 1 was adapted and expanded upon from Schwabe, Joëls, Roozendaal, Wolf, & Oitzl, 2012.