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Early care experiences and HPA axis regulation in children: a mechanism for later trauma vulnerability

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Abstract

Post-traumatic stress disorder (PTSD) is associated with functional abnormalities of the hypothalamic- pituitary-adrenocortical (HPA) axis. Emerging evidence suggests that failures in social regulation of the HPA axis in young children manifested as neglectful or abusive care may play a role in shaping cortico-limbic circuits involved in processing experiences threatening experiences encountered later in life. Low cortisol levels, particularly near the peak of the diurnal rhythm, have been reported in abused, neglected and deprived children. Thus early imprinting effects of parenting quality on the HPA system regulation may be one of the mechanisms causing heightened risk of PTSD in responses to later trauma. However there is also evidence that the altered patterns of cortisol production seen in the context of early adverse care are not permanent, and remit once the care children receive improves. What awaits study is whether periods of atypical cortisol levels and altered HPA function early in life, even if transient, impact brain development in ways that heighten vulnerability to PTSD in response to traumas experienced later.

Keywords

stress; early experience; cortisol; children

Post-traumatic stress disorder (PTSD) develops in only a subset of individuals who experience trauma. Hyper-arousal of threat-responsive neurobiological systems, including the sympathetic nervous system, and hypo-arousal of the hypothalamic- pituitary-adrenocortical (HPA) system at the time of trauma exposure are hypothesized to represent pre-existing risk factors for the development of PTSD (for review, see Delahanty and Nugent, 2006). Hypo-activity of the HPA axis is believed to enhance risk of PTSD perhaps through failing to counter-regulate hyper-arousal in other trauma-sensitive neurobiological systems (Yehuda, 2001). In adults, prior trauma increases both the risk of PTSD and the risk of blunted cortisol responses to trauma (Delahanty and Nugent, 2006). Exposure to trauma during childhood is believed to be particularly critical in increasing the risk of PTSD in response to later traumatic experiences (Teicher et al., 2002). In studies predicting PTSD from early childhood experiences, however, measures of childhood trauma include a range of experiences from sexual abuse to more subtle forms of emotional abuse (Yehuda, 2002). Furthermore, the animal models used to support arguments that childhood abuse shapes vulnerability to developing PTSD do not clearly point to childhood trauma as a necessary

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antecedent (Heim et al., 1997). Rather, they point to lack or loss of expectable parental stimulation as critical in altering the development of the HPA axis and neurobiological systems involved in regulating reactions to stressful and traumatic events (Gunnar and Fisher, 2006).

In the following review we will examine the impact of variations in parental care on activity of the HPA axis in animal models and young children. Our focus on the HPA axis is based on the putative role of this neuroendocrine system in the etiology of PTSD (Yehuda, 2001). We will argue that parental care provides a social regulator of activity of the HPA axis in infants and young children (Gunnar and Donzella, 2002). Disturbances in parental care, thus, disrupt normal regulation of this neuroendocrine system. However, the effects of these disruptions are varied. In some instances, disturbances in the typical circadian rhythm of the axis are observed, in others the presence of the caregiver fails to buffer activation of the axis in response to events that produce fearful behavior, while in still others the parent's presence and interaction with the child stimulates elevations in cortisol. Whether these different effects on HPA axis activity reflect common or varied elements in the parent–offspring relationships are not yet known. However, there is now substantial evidence that parental care impacts activity of the HPA axis in the young of many species, including our own. As such, this evidence supports arguments that failures in the caregiving system may increase the risk of PTSD through altering the development of stress- and threat-responsive neurobiological systems. This review assumes the reader's knowledge of the neuroana tomy and physiology of the HPA axis (for review, see de Kloet, 1991; Herman et al., 2005) and mechanisms through which altered activity of this axis may impact neurodevelopment (for review, see Gunnar and Vazquez, 2006).

Animal models: parental care and HPA activity

Much of the animal work has been conducted on rats. During infancy (postnatal days 4–14) rats exhibit low basal levels of corticosterone (the predominant steroid hormone produced by the HPA axis in rodents) and hypo-responsiveness of the HPA axis to many stressors (Rosenfeld et al., 1992). This hypo-responsive period in rats is maintained by specific components of maternal care: licking and grooming and the delivery of milk into the gut (Suchecki et al., 1993a, b, 1995). Both manipulations that alter licking and grooming and normal variations in this aspect of maternal care produce long-term alterations in the HPA axis and in emotional behavior. Short (3–5 min) repeated daily separations in infancy result in the development of attenuated HPA reactivity and fearfulness to stressors encountered later in life. In contrast, longer separations (e.g., 180 min daily) produce the development of a more hyper-responsive HPA axis and a more fearful animal (for review, see Sanchez et al., 2001). Repeated, prolonged separations also produce numerous other alterations that support vulnerability to stressors throughout life (Cirulli et al., 2000, 2003; Roceri et al., 2004). Early, repeated separations are believed to produce their effects, in part, through altering maternal care: increasing maternal licking and grooming in the case of brief, daily separations and reducing maternal licking and grooming in the case of prolonged daily separations (Heim and Nemeroff, 2001; Denenberg, 1999; Tang et al., 2006).

The argument that parental care mediates the impact of early separations is enhanced by evidence that normal variations in maternal licking and grooming produce the same effects as early separations. When the offspring of high licking and grooming dams are followed, they exhibit better regulation of the HPA axis and reduced fearful behavior in adulthood (Caldji et al., 1998). These effects are not due to common maternal and offspring genetics, as they can be produced in pups cross-fostered from low-to-high licking and grooming dams (Francis and Meaney, 1999). Furthermore, there is now good evidence that maternal care in rats produces long-term impacts on stress and emotional behavior through affecting methylation of the glucocorticoid receptor (GR) gene in the hippocampus. This gene produces the GR, the receptor that is critically involved in negative feedback of the HPA axis in response to psychosocial stressors (De Kloet, 1991). In response to low maternal care (i.e., low licking and grooming), there is greater methylation of the GR gene which results in fewer glucocorticoid receptors in the hippocampus and poorer negative feedback regulation of the HPA axis (Meaney and Szyf, 2005). Pharmacological intervention can correct these impacts on GR methylation. Thus offsprings of low licking and grooming dams who were centrally infused with methionine showed a reversal of the effects of maternal behavior on the fearful behavior, HPA axis regulation and GR methylation (Weaver et al., 2005). Postnatal experiences can also alter some, but not all of these effects. Thus exposure of juvenile rats to an enriched environment prevents expression of the heightened fearfulness and elevated corticosterone in response to stressors, but it does not alter patterns of GR methylation, suggesting that these animals may maintain a vulnerability to traumatic stimulation later in life (Francis et al., 2002).

In non-human primates, the work on early parental care has progressed through the lens of attachment theory. Through this lens, the mother–infant relationship is viewed as a stress buffer (Bowlby, 1969; Suomi, 1995). The natural ecology of most primate species is social. Mother and infant live in troupes that include other mothers and infants, adult males and the infant's older siblings. Species differ in how often the infant is parented by other members of the troupe — a phenomenon termed alloparenting or aunting. Although the availability of alloparents does not prevent elevations in cortisol to maternal separation, it does result in a more rapid termination of the HPA response and a reduced likelihood that despair behavior will develop during prolonged separations (Levine and Wiener, 1988). Thus, in primate infants maternal buffering is a function that can be provided to some extent by other nurturing conspecifics.

While repeated prolonged separations in rats may produce hyper-cortisolism, in monkeys they may reduce HPA activity (Levine et al., 1997; Dettling et al., 2002; Sanchez et al., 2005). In rhesus macaques, patterns of low basal output of cortisol following repeated separations have been accompanied by evidence of heightened startle responses (Sanchez et al., 2005), a pattern reminiscent of PTSD. Similarly, manipulations like variable foraging that produced disturbed mother–infant relations do not necessarily produce hyper-activation of the HPA axis in adulthood. Nevertheless, animals reared in these paradigms do exhibit elevated corticotropin-releasing hormone (CRH) in cerebrospinal fluid, altered serotonergic and noradrenergic activity and fearful behavior (Rosenblum and Andrews, 1994). Likewise, animals reared under conditions of parental deprivation as adults do not exhibit heightened HPA responses to stressors or neurochemical and structural changes in the HPA system (for

review, see Sanchez et al., 2001), but do exhibit changes in monoamine systems (Kraemer et al., 1989), hippocampal development (Siegel et al., 1993) and in CRH receptors in the prefrontal cortex and amygdala (Sanchez et al., 1999). These differences from the rodent model likely reflect the greater maturity of the HPA axis at birth relative to its maturity in the rat (Gunnar and Vazquez, 2006). To summarize, in non-human primates parental care is a potent regulator of activity of the infant's HPA axis; however, hyper-reactivity of the axis as a consequence of adverse early care has typically not been observed. Despite a general failure to observer hyper-reactivity of the axis following adverse early care experiences, in non-human primates many of the anxiety-associated behavioral and neurobiological sequelae of disturbances in early parental care have been observed.

Human development and the hypothalamic-pituitary axis

With these animal data in mind, we turn now to data on parental care and activity of the HPA axis in human infants and children. These data, however, must be viewed in the context of developmental changes in HPA axis activity. We will describe these changes first.

Development of HPA activity during childhood

The HPA axis is highly responsive to stressors at birth; indeed, HPA stress responses are observed by as early as 18–20 weeks of gestation (Giannakoulopoulos et al., 1999). In adults, approximately 80% of circulating cortisol is usually bound to corticosteroid-binding globulin (CBG) and is thus rendered biologically inactive. However, CBG levels are low in the human newborn and do not achieve adult levels until about 6 months (Hadjian et al., 1972). As a result, plasma levels of total cortisol are low in the newborn and increase over the first months of life; while the free fraction of the hormone is as high or higher than levels observed in older infants and children (Gunnar et al., 1988). In addition, when salivary measures of cortisol are used which reflect only the free fraction of the hormone, newborns show marked elevations in cortisol to even very minor perturbations (e.g., undressing, weighing and measuring; Gunnar et al., 1992). Therefore, by 6 months of age, the HPA system of the human child is relatively mature.

Over the first year of life, the human HPA system becomes progressively less responsive to stressors (Gunnar et al., 1996). Indeed, by one year of age it becomes difficult to elevate cortisol to a variety of events, which nonetheless, elicit significant behavioral distress (Ramsay and Lewis, 1994; Gunnar and Donzella, 1999). As will be discussed below, this apparent hypo-responsivity of the HPA axis reflects the fact that during the first year of life the human HPA axis comes under strong social regulation or parental buffering (Gunnar and Donzella, 2002). During childhood, small increases in cortisol can be observed to the experimentally induced stressors (Blair et al., 2005), although in most cases only some children exhibit these elevations (Talge et al., 2007). Likewise, stressors such as the beginning kindergarten or a new school year and important school exams produce cortisol increases in some children (Boyce et al., 1995; Spangler, 1995; Davis et al., 1999; Bruce et al., 2002).

Epidemiological data indicate that onset of stress-related emotional disorders increases during adolescence (Angold and Rutter, 1992). It has been suggested that this heightened

vulnerability to stressors may reflect increased reactivity of the HPA axis and other neurobiological changes over the transition to adolescence (Spear, 2000). There is now good evidence from both cross-sectional and longitudinal studies that basal cortisol levels increase as children progress into adolescence, perhaps related to pubertal changes (Gunnar and Vazquez, 2006). Indeed, a recent study found that adolescents at higher stages of pubertal development had more elevated overall diurnal cortisol curves reflected in cortisol levels sampled throughout the day (Adam, 2006). Several studies now suggest that over the pubertal transition the HPA system becomes more adult-like in its responses to stressors (Gunnar, in preparation; Stroud, in preparation). It thus seems likely that the impact of early care experiences on stress reactivity and regulation may not be fully evident until after the pubertal transition.

Normative variations in parental care

As in research on non-human primates, regulation of the human infant's HPA system has been viewed through the lens of attachment theory. By the end of the first year, infants develop strong attachment relationships with one or a few consistent caregivers (Bowlby, 1969). The attachment figure provides a source of comfort and stress modulation. Patterns of behavior in response to mildly stressful provocation (stranger approach and brief separations) have been described which presumably reflect differences in the child's sense of security in the attachment relationship (Ainsworth et al., 1978). Secure relationships are characterized by caregivers that are consistently responsive and sensitive to their children's needs for both exploration and reassurance (Ainsworth et al., 1978). Thus, both parental sensitivity/ responsiveness and patterns of infant attachment behavior have been examined as a means of examining the parental buffering hypothesis in humans.

In general, both parental sensitivity/responsiveness and secure attachment relationships buffer the child's HPA axis in response to stressors. For example, Nachmias et al. (1996) exposed 18-montholds to a series of events that elicited wary or fearful reactions in approximately half of the participants. Elevations in cortisol, however, were only observed in fearful toddlers who were insecurely attached to the parent who was with them during testing. Ahnert et al. (2004) examined cortisol responses of toddlers when they visited a new child care center in the presence of their mothers. In their mother's presence, but not during the child's initial days without mother at child care, securely attached infants exhibited markedly lower cortisol elevations compared to insecurely attached toddlers. In several studies, Spangler has demonstrated elevations in cortisol only among insecurely but not securely attached infants (for review, see Spangler and Grossmann, 1999).

Insensitive patterns of parental care early in the first year of life also predict larger cortisol responses to stressors (Gunnar et al., 1996). Indeed, when mothers were asked to play with their infants, infants with more sensitive mothers exhibited decreases in cortisol over the play period, while those with less sensitive mothers exhibited small increases in cortisol (Spangler et al., 1994). Harsh parenting (spanking) has also been shown to predict larger cortisol responses to mildly stressful events in infants (Bugental et al., 2003). Furthermore, when provided (randomly) with a sensitive and responsive surrogate caregiver, even 9-month-old infants with negative emotional temperaments did not show a cortisol elevation to

30 min of maternal separation; while those given an insensitive, unresponsive surrogate caregiver did (Gunnar et al., 1992). Similar findings have been obtained for toddlers and preschoolers in full-day out-of-home childcare (for review, see Gunnar and Donzella, 2002). These data support the hypothesis that children who experience less supportive and responsive care may frequently experience stressor-induced elevations in cortisol that might, over time, impact neurobehavioral development (see also De Kloet et al., 1996).

Studies of “at risk” children also support the argument that early care may have long-term impacts on vulnerability to stressful or traumatic events. A number of studies have been conducted on children whose mothers experience postpartum and/or major depression in the child’s first years of life. During bouts of clinical depression, mothers are typically less responsive and more rejecting with their infants and young children (Ashman et al., 2002). Because bouts of clinical depression are associated with disturbances in parenting, associations between when the mother was depressed during the child’s development and child outcomes provide a window into the timing of disturbances in parental care and neurobehavioral development.

Preschoolers whose mothers have a history of clinical depression or who report high number of depressive symptoms during the child’s first 2 years, exhibit elevated home cortisol levels, particularly in the context of on-going stress in the family (Dawson and Ashman, 2000; Essex et al., 2002). School-aged children exposed to more prolonged periods of maternal depression in infancy and early childhood have been noted to have higher and more variable early morning cortisol levels even after controlling for maternal depression later in the child’s life (Halligan et al., 2004; Lupien et al., 2000). It is not clear, however, whether maternal depression during a child’s early development increases reactivity of the HPA axis, as this has been noted only for girls and then only for girls with concurrent internalizing behavior problems (Ashman et al., 2002). Several of these studies implicate elevated cortisol levels in the etiology of internalizing problems in childhood (Smider et al., 2002) and the emergence of depression in response to stressful events during adolescence (Halligan et al., 2007) for the offspring of depressed mothers. Unfortunately, although maternal depression has often been shown to be correlated with less sensitive and responsive care (Dawson and Ashman, 2000), in none of these studies was parental care examined as a mediator of the impact of maternal depressive symptoms on HPA axis activity. Furthermore, they do not allow us to disentangle genetic vulnerabilities in children of depressed mothers from the impact of postnatal care. That is, we do not know whether bouts of disturbed parental care would have the same impact on children who did not have a high genetic load for depression.

To summarize, studies of variations in parental care within the normal range in humans strongly indicate that less sensitive and responsive caregiving is associated with poorer concurrent regulation of the HPA axis in children. Sensitive and responsive care and associated secure attachment relationships appear to provide a powerful buffer for the HPA axis during early development. Children exposed to less sensitive/responsive care and those of mothers who use more harsh (though not necessarily abusive) discipline practices exhibit higher basal cortisol levels and their mother’s presence does not prevent elevations in cortisol to the type of everyday stressors experienced by young children. Studies of the

offspring of depressed mothers appear to indicate that these early care experiences may produce permanent alteration in HPA axis functioning. However, because the children of depressed mothers may have inherited genes that increase their vulnerability to variations in maternal care, it is difficult to know whether we can extrapolate these findings to children with different genetic heritages.

Severe deprivation, neglect and abuse

Thus far we have reviewed human studies examining care experiences, which though not perhaps optimal, would not reach criteria for maltreatment. Unfortunately for comparisons with animal studies, HPA reactivity to stressors has not yet been studied in children exposed to severe deprivation, neglect and abuse (see Heim et al., 2004, for such studies of adults exposed to abuse during childhood). Instead, the focus in the child research has been on basal activity of the axis. Evidence for both elevated and extremely low cortisol levels have been obtained. When extremely low levels have been noted, these have most often been seen in early morning, near the peak of the circadian rhythm (Gunnar and Vazquez, 2001). Because the diurnal slope of cortisol is largely determined by the height of the early morning peak, children with the extremely low morning levels have a flat daytime cortisol rhythm. Whether suppressed or elevated basal cortisol levels are noted, however, may depend on the age of the child, the type of maltreatment, whether the maltreatment is on-going and how long it has been since the child was placed in more supportive care arrangements.

There are now several studies of preschool-aged children in foster care that reveal quite different patterns of HPA axis functioning than those noted in studies of children of depressed mothers. Dozier et al. (2006) found that approximately 40% of their sample of foster preschoolers exhibited extremely low early morning cortisol levels, while about 20% exhibited markedly high levels relative to children living in non-maltreating families. Bruce et al. (under review) noted similar findings and also found that prior neglect, rather than abuse, predicted low early morning levels. In a study following preschoolers in foster care, children in regular foster care increasingly exhibited low early morning levels over time (Fisher et al., 2007). These children also were more likely than children of the same social class living with their non-maltreating parents to develop insecure patterns of attachment over this time period (Fisher et al., in press). These results are consistent with data on toddlers living in institutions (i.e., orphanages). Orphanage-reared children also have very low early morning cortisol levels and a relatively flat pattern of cortisol production over the day (Carlson and Earls, 1997). Institutional care tends to be characterized by little individualized care, low levels of adult–child interaction, but especially among infants and toddlers, little frank physical or sexual abuse (Zeanah et al., 2006). Benign neglect is a term used to typify institutional care of infants and young children, and hence these data appear remarkably similar to the results reported for preschool-aged children in foster care.

The findings for children exposed to significant neglect and deprivation are also similar to reports of hypo-cortisolism among adults who experience chronic stress (Heim et al., 2000). One mechanism invoked to explain the development of hypocortisolism is down-regulation of the HPA axis at the level of the pituitary in response to chronic CRH drive (Fries et al., 2005). Accordingly, one might expect that prior to appearance of very low early morning

cortisol levels, there might be a period of exceptionally high cortisol (Fries et al., 2005). Unfortunately, most of the children examined in both the foster care and institutional care studies experienced adverse care from birth. Examining such children earlier in their care histories also means examining them when they are infants. We have already noted the marked changes in HPA axis activity over the course of the first year or two of life. Developmental change and duration of exposure to maltreatment are difficult to disentangle. Notably, however, the one foster care study examining infants, as opposed to preschoolers, reported exceptionally high cortisol levels for infants in regular foster care relative to infants of the same social class living with their non-maltreating parents (Dozier et al., in press).

There is little reason to believe that this hypocortisolism in basal activity of the HPA axis observed early in life in the context of neglect and deprivation is permanent. At least in work with adults, low cortisol output can be reversed by alleviating chronic stress conditions (for review, see Fries et al., 2005). Among infants in foster care, training foster parents to be more sensitive to the needs of previously neglected and abused infants results in normalization of basal cortisol levels with only 10 weeks of parent training (Dozier et al., in press). What is not clear is whether alterations in HPA axis activity persist once children have time to recover in more supportive care arrangements. In addressing this question we will not cover studies of children with chronic PTSD (Carrion et al., 2001, 2002; De Bellis et al., 1999a, b), although we will consider whether current psychiatric morbidity might explain associations between early care experiences and later HPA activity.

Two studies have now examined basal cortisol levels in children adopted from institutions. For children adopted from the type of global deprivation that characterized Romanian institutions in the early 1990s, elevated rather than suppressed cortisol levels were noted 6–7 years post-adoption (Gunnar et al., 2001). Most of these children were severely growth delayed at adoption due to poor health, nutrition and social stimulation in the orphanage (Rutter, 1998). In a subsequent study, growth delay at adoption rather than duration of institutional care or growth parameters at assessment predicted elevated early morning cortisol levels (Kertes et al., 2007). In this latter study, very few of the children who were growth delayed at adoption met criteria for internalizing problems at assessment; thus, it was unlikely that concurrent psychopathology moderated the relations between early care, growth delay and basal cortisol. Studies of maltreated children suggest that only those who experience the most severe and prolonged maltreatment may have elevated cortisol levels (Cicchetti and Rogosch, 2001a; De Bellis et al., 1999a). However, these factors also increase the risk of both affective and conduct disorder, and thus cortisol levels and psychopathology are difficult to disentangle (Cicchetti and Rogosch, 2001b). Even after their maltreatment has been exposed and child protective services are involved, on-going stress in the family, rather than maltreatment history, may explain increased HPA activity in the children (Kaufman et al., 1997).

Taken together, the studies of post-institutionalized children and children with maltreatment histories do not suggest that for most children, periods of adverse early care increases the basal set point of the HPA axis. Lack of a persistent increase in basal cortisol levels pursuant to early life stress would be consistent with findings in the animal literature where HPA reactivity but not basal levels appear to be affected. When early life stress results in long-

term increases in basal HPA levels even after the conditions producing the stress have been improved, the child either appears to have experienced growth failure due to the stressful conditions or, as in the data on children of mothers with depression, may carry a high genetic load for depression or other affective disorders. However, because there are no studies on HPA stress reactivity in children exposed as infants to adverse care, we cannot conclude that their early experiences failed to impact how the axis responds to stressors later in development. This, rather than long-term changes in basal activity is what has been noted in the early experience animal literature and this is what remains to be studied in children exposed to significantly adverse care early in life. Obviously, studies of HPA axis stress reactivity pursuant to early deprivation and maltreatment are crucial to fully understanding how early parental care may impact vulnerability to PTSD. However, because a fully adult-like patterns of HPA responses to stressors may not emerge until sometime in adolescence, studies of the impact of adverse care on subsequent HPA responses to stressors will need to take into account the child's developmental level.

Conclusions

Pre-clinical human studies, animal models and recent studies with children deprived of adequate parenting provide evidence that the HPA axis is under strong social regulation early in life. Accordingly, variations in parental care have potent effects on concurrent regulation of the axis. Unlike in studies of rats, however, in neither non-human primates nor human children do early adverse care experiences appear to produce permanent alterations activity of the HPA axis. The exceptions to this conclusion can be found in studies of children of depressed mothers, children whose early care produced severe physical growth delays, and in children who develop chronic PTSD. Few studies of human children exposed to adverse early care have examined HPA responses to laboratory stressors or to real-life traumatic events. These studies are needed. Failure to observe long-term alterations in HPA axis activity in humans does not mean that failure of the caregiving system to provide regulation of this axis early in development is of no consequence. Rather, as in nonhuman primates, it may suggest that the HPA axis, being relatively mature at birth, is less susceptible to the long-term alterations noted in studies of infant rats. Nonetheless, failures in social regulation of the HPA axis in young children because of inadequate and/or abusive care may play a role in shaping cortico-limbic circuits involved in processing traumatic experiences. Evidence for this hypothesis, however, will require finding disturbances in HPA activity in early childhood that are reversible by the provision of more supportive care, but that nevertheless predict the development of individual differences in neurobiological systems associated with risk for PTSD. Longitudinal studies of this sort are just beginning to be conducted (Dozier et al., in press; Fisher et al., under review).

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Abbreviations

CBG	corticosteroid-binding globulin
CRH	corticotropin-releasing hormone
GR	glucocorticoid receptor
HPA	hypothalamic-pituitary-adrenocortical
PTSD	post-traumatic stress disorder

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