From attachment to independence: stress hormone control of ecologically relevant emergence of infants' responses to threat

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Young infant rat pups learn to approach cues associated with pain rather than learning amygdala-dependent fear. This approach response is considered caregiver-seeking and ecologically relevant within the context of attachment. With maturation, increases in the stress hormone corticosterone permit amygdala-dependent fear, which is crucial for survival during independent living. During the developmental transition from attachment to fear learning, maternal presence suppresses corticosterone elevation to block amygdala-dependent fear learning and re-engage the attachment circuitry. Early life trauma disrupts this developmental sequence by triggering a precocious increase of corticosterone, which permits amygdala-dependent threat responses. In this review, we explore the importance of the stress hormone corticosterone in infants' transition from complete dependence on the caregiver to independence, with consideration for environmental influences on threat response ontogeny and mechanistic importance of social buffering of the stress response.

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Introduction

Pioneering research on infant-caregiver dyads, which began in the mid 1900's, highlights stress as a major mediator of infant caregiving quality/experiences and is critical in programming neurobehavioral development [1,2]. Importantly, it was the combined insights from clinical and basic scientists, with diverse research areas across many species, that linked disturbed maternal care/separation and compromised threat response functioning [1,3,4]. This concept of stress as a mediator between infant experiences and programming of neurobehavioral function is still prevalent today and has been documented in many diverse species [5–7].

The stress hormone corticosterone is typically thought of as damaging to infant behavioral and neural development [8,9]. However, it is now clear that corticosterone is also critically important for normal brain development and normal infant neurobehavioral functioning [10,11]. Here we review the effects of corticosterone within the context of normal development using infant rat fear/threat learning and expression as a framework. The behavioral neurobiology of threat response is relatively well-defined, especially in the rodent and is a useful template to explore how corticosterone modulates the neurodevelopment of fear/threat learning and expression. While differences exist between humans and rodents in the stage of neurodevelopment at birth [12], we focus here on the experience-dependent learning and how it shapes threat response behaviors that are phylogenetically conserved among species and provide an important bridge for translating rodent and nonhuman primate findings to humans' [6,13,14].

In adults of many diverse species, threat presentation will prompt a defensive threat response specific to the environment and threat intensity: in rats and humans, these responses can range from hiding, freezing, fleeing or attack. As we explore the development of threat response and its modulation by corticosterone, it is important to consider the ecological context of this behavior as the infant transitions from complete dependence to independence. Altricial animals, such as the rat and human, require extensive caregiving to survive. A reciprocal bond between the infant and caregiver, termed attachment, must be learned by both to maintain this close contact. Infants of most altricial species are physically incapable of defending themselves from predators. Accordingly, an infant of altricial species will typically seek the caregiver for protection, and only later, begin to attack a predator or freeze. This review will discuss the neurobiology that supports this ecologically and age-appropriate change in fear/threat response and how this developmental switch is controlled by corticosterone to produce adaptive behaviors during early development.

Ontogeny of innate fear expression: modulation by corticosterone

In altricial species, very young infants confined to the nest depend entirely on their caregiver for protection. The expression of fear changes during maturation in ways that are appropriate to the developmental stage and ecological niche of the animal: the infant rat pup does not freeze to predator odor until it begins to crawl out of the nest [15]. For a rat, these brief excursions begin around postnatal day (PN) 10 [15], at which point the amygdala becomes functionally integrated to support innate species-specific defensive responses to predator odor, such as freezing [16–19]. Initially, it was thought that this reflected maturation of the amygdala at PN10: this, however, turned out not to be the case. While amygdala development is protracted and continues through adolescence, major nuclei of the amygdala become visible and support plasticity days before the amygdala begins to support threat response behavior [20,21], provided sufficient levels of corticosterone are present in the amygdala [22,23]. The importance of maturation of the hypothalamic-pituitary-adrenal (HPA) axis and increased corticosterone levels in shaping the ontogeny of threat response was uncovered by Takahashi, who found that an increase in corticosterone in younger animals enables freezing to predator odor [24]. Adrenalectomy at PN10 prevents development of freezing behavior, which can be reinstated by delivering exogenous CORT (Figure 1) [18].

Figure 1
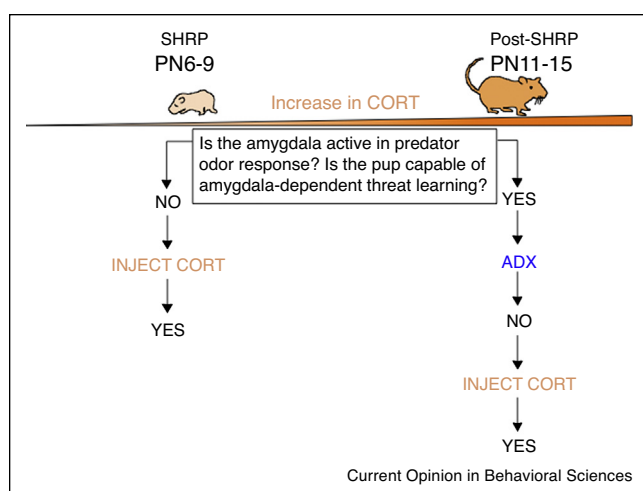
Corticosterone control of amygdala-dependent threat response and threat learning in development. During the stress hyporesponsive period (SHRP) that occurs prior to PN10, corticosterone (CORT) levels are low and the amygdala is unresponsive to predator odor as well as odor cue conditioning. This result is also observed in older pups that have received adrenalectomy, and is reversed by injecting exogenous CORT. In pups older than PN10, the amygdala is responsive to predator odor and supports fear conditioning. This is also observed in pups as young as PN6, if exogenous corticosterone is injected into the amygdala.

Thus, in order to understand the impact of corticosterone on the developing brain, it is important to first consider the ontogeny of the HPA axis, which undergoes considerable changes in most altricial species. The period of reduced stress-induced corticosterone release prior to the age of PN10 has been termed the 'stress hyporesponsive period' (SHRP). Gradual increase in basal corticosterone levels over the course of this period reaches a critical threshold at PN10 to terminate the SHRP and permit the amygdala to become active with exposure to predator odor [25]. The SHRP is observed at multiple levels of the HPA-axis, including blunted pituitary adrenocorticotropic hormone (ACTH) secretion, decreased sensitivity to corticotropin-releasing hormone (CRH) and an adrenal gland hyporesponsive to circulating ACTH levels [26]. Thus, the stress hormone corticosterone plays two roles in defining the neurodevelopment of threat response: 1) gradual increases in endogenous corticosterone reach a critical threshold and 2) an acute threat (shock or predator odor) will produce an immediate increase in stimulus-evoked corticosterone. Together, this change in the stress system permits the switch to trigger a specific threat response.

Research from our lab and others expanded on Takahashi's to show that either ontogenetic or experimentally manipulated changes in corticosterone level control whether the amygdala is activated by predator odor, as measured by c-Fos expression. Fear is expressed if the amygdala is functionally activated by corticosterone, while decreasing corticosterone results in suppressed amygdala activity and blocked fear expression [17,27]. Importantly, corticosterone acts as a switch with the power to activate the amygdala to permit fear expression. While circadian regulation of corticosterone causes fluctuations in baseline corticosterone levels throughout the day, importantly, this fluctuation in corticosterone does not appear to have a detectable impact on the control switch that induces amygdala activation and threat response, since threat responses occur regardless of the time of day.

Ontogeny of learned fear

In addition to innate, naturally occurring threats in the environment, animals also learn to tag stimuli in the environment with threat value, which provides a necessary substrate for behavioral plasticity. Learning about threat is phylogenetically conserved and is supported by a relatively simplistic circuit that appears homologous across mammalian species. Threat learning is a rapid, robust form of classical conditioning, where a neutral conditioned stimulus (CS; e.g. tone or odor) is paired with an aversive unconditioned stimulus (US; e.g. electric shock). After temporal pairing of the CS-US, an associative link between CS and US causes the neutral CS to take on threat value [28,29]. Once a CS takes on the threat value, the animal will show defensive/fear responses to

presentations of the CS, even in the absence of the US. These threat responses are typically similar in form to responses to predator odor.

As we explore the development of learned fear responses, we will highlight the role of corticosterone in supporting ecologically adaptive behaviors as the infant transitions from complete dependence on the caregiver to independence [15,16,30,31]. The ability to tag stimuli with threat value is absent during the SHRP until PN10 [15,30]. As is the case for innate fear expression discussed above, the ontogenetic delay is due to the failure of the amygdala to become functionally active in response to threat [16]. Indeed, in PN10 pups and older, pairing odor with moderate shock (0.5 mA to the tail or foot) will activate the amygdala and support fear/threat learning [16]. A causal link between fear/threat learning and the amygdala is revealed by experiments in which pharmacological suppression of the amygdala in older pups ($\geq$ PN 10) will block odor-shock threat/fear learning, although this manipulation has no effect on pups still too young to engage in amygdala-dependent fear learning [32]. Likewise, tetanic stimulation of the basolateral amygdala does not induce long-term potentiation in pups younger than PN10, in contrast to older pups [33]. Together, these studies suggest that activation of the amygdala is causal to support associative fear learning in pups older than PN10, thus representing the functional emergence of the amygdala in threat response at that time point.

As discussed previously, basal corticosterone levels increase over the course of the SHRP of postnatal development. By PN10, basal corticosterone increases sufficiently to reach a threshold for engaging learning plasticity within the amygdala during odor-shock conditioning [34]. Bilateral amygdala administration of corticosterone in PN8 pups will prematurely induce amygdala plasticity in response to odor-shock conditioning and support fear/threat learning [23]. However, in pups younger than PN6, the amygdala is too immature to support odor-shock conditioning, even with corticosterone injection into the amygdala. Conversely, intra-amygdala blockade of corticosterone receptors in older pups (PN10-15) is sufficient to suppress amygdala activation and abolish odor-shock fear/threat conditioning [23] (Figure 1). Thus, between the ages of PN6 and PN15, corticosterone is necessary and sufficient to support both amygdala plasticity and subsequent fear/threat learning.

During the SHRP of early development (PN < 10), pups paradoxically prefer to approach a conditioned stimulus (e.g., neutral odor, such as peppermint) that has been paired with a painful stimulus [31,35–37]. Indeed, a shock-paired odor becomes powerful enough to support social interactions with the mother, including nipple attachment, which otherwise requires maternal odor. Neither failure of the pup to detect pain or varied

Figure 2
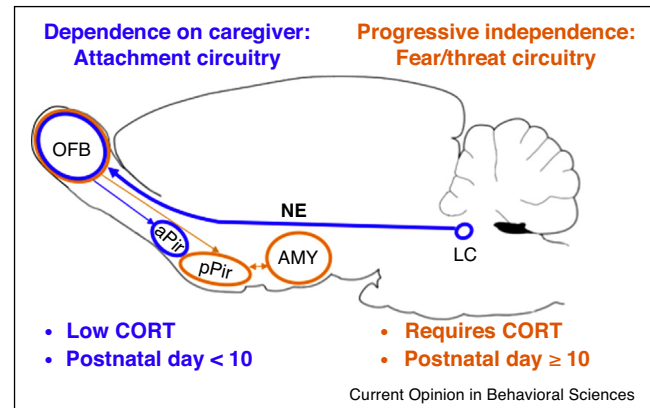
Corticosterone acts as a control switch between attachment circuitry and amygdala-dependent threat response. In pups younger than PN10, high levels of norepinephrine (NE) are secreted by the locus coeruleus (LC) into the olfactory bulb (OFB), thus activating learning-induced changes in the OFB and anterior piriform cortex (aPir) to support attachment to the caregiver. As corticosterone (CORT) levels increase at PN10, the OFB will respond to threats likely by co-activation of the posterior piriform cortex (pPir) and amygdala to produce an independent defensive response, such as freezing. Between PN10-15, maternal presence will socially buffer threats to the pup, thus reducing pup corticosterone, suppressing amygdala activity and eliminating the independent defensive response.

threshold for pain explain this pain-induced odor preference [38,39]. Importantly, odor-shock conditioning in pups during the SHRP does not functionally activate the amygdala threat response circuitry. Instead, this paradoxical preference is under control of the unique neurobiological circuitry for attachment learning: the olfactory bulb, anterior piriform cortex, and hyperfunctioning noradrenergic locus coeruleus (Figure 2) [40–42]. During the SHRP, when corticosterone levels are low, increases in norepinephrine (NE) are integral for forming pup-caregiver attachment [40]. Noradrenergic cell bodies located in the locus coeruleus send axons to innervate the mitral-tufted cells of the olfactory bulb with NE [43,44]. In young pups, this produces learned attachment-related odor preferences and learning-induced plasticity in the bulb and piriform cortex [45].

Ecological significance of the late emergence of threat learning

Why would it be advantageous for pups to have a delayed onset for fear/threat learning? For species that require parental care for survival, infants must learn rapid and robust attachment to their caregiver, regardless of the quality of care that they receive [46]. As stated above, abused pups paradoxically approach cues associated with maltreatment [47,48]. Importantly, odor-shock conditioning in pups during the SHRP of early development (PN < 10) does not functionally activate the adult-like fear/threat circuit, but rather engages the age-dependent

learning circuit critical for survival in young pups—the attachment neural system used by pups to learn about and attach to the caregiver. Typical maternal behaviors, such as pup retrieval or entering/leaving the nest, are at times associated with brief painful stimuli as the dam occasionally handles pups roughly or tramples them [46,48]. Pup survival depends on strong, learned attachment to the caregiver, and any associative learning such as odor-pain associations with the caregiver, could pose a threat to this bond. Thus, delayed onset of amygdala dependent CS-US learning may have evolved to prevent pups from avoiding the caregiver, regardless of the quality of care.

In summary, the stress hormone corticosterone has an adaptive role in defining pup's immediate neurobehavioral response. The gradual increase in endogenous corticosterone over early neurodevelopment together with the stimulus-evoked increase in corticosterone control the development of pup threat response behavior, thus ensuring adaptive and ecologically appropriate response to threat. This illustrates the important role of this stress hormone in producing adaptive behaviors [10].

Maternal social buffering of corticosterone response

Next, we will describe a system controlled by corticosterone that enables pups to rapidly and repeatedly switch back and forth between the immature attachment behavior of younger pups in the nest and the more mature freezing behavior of the older pups (Figure 3). Understanding the immediate effects of corticosterone on developing pups requires an understanding of how maternal presence modifies pups' corticosterone levels [5]. This is termed 'social buffering' and is observed in many species and across development [49–51]. Social buffering has robust beneficial effects by reducing pain and anxiety while enhancing healing in both humans and rats [5,52–56].

Previous work has shown that maternal presence is sufficient to block pain-induced increases in corticosterone [57]. Due to the critical role of corticosterone in turning on and off fear conditioning in pups, we explored whether naturalistic control of corticosterone by social buffering could control rapid switching between fear/threat learning and attachment learning in pups. Indeed, our lab has found that mother's presence controls pups' shock-induced preference vs. aversion learning. As illustrated in Figure 3 we have termed this brief developmental period the Transitional Sensitive Period, which extends from PN10 through PN15 in typically developing pups [22]. Specifically, maternal absence during odor-shock conditioning in pups at PN10-15 functionally activates the amygdala and induces a strong aversion to the conditioned odor. However, if this same conditioning takes

Figure 3
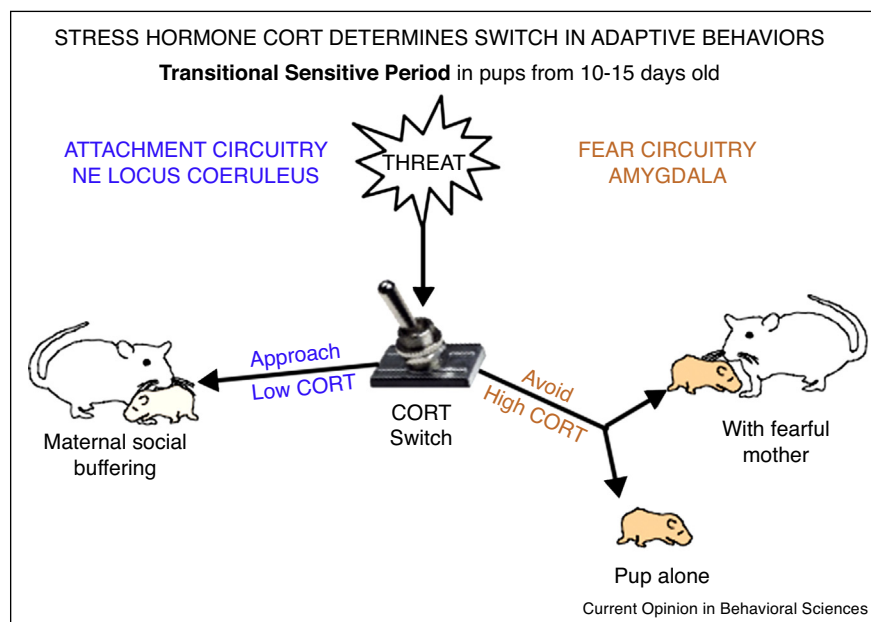
Maternal control of corticosterone determines rapid and responsive switch in adaptive threat response behaviors during the Transitional Sensitive Period (PN10-15). Pup corticosterone (CORT) levels in response to threat are under maternal control between PN10-PN15. In the presence of a mother that perceives no threat, pups corticosterone levels are low and attachment circuitry is active: norepinephrine (NE) is released by the locus coeroeleus (LC) to produce the paradoxical behavior wherein pups approach a conditioned odor stimulus paired with shock. If the mother is fearful, she emits an alarm pheromone, which increases pup corticosterone and activates the amygdala dependent threat-response circuitry: the pup will then avoid conditioned odor stimulus paired with shock. This corticosterone induced amygdala dependent threat response is also observed when pups are alone.

place in the presence of the mother, amygdala plasticity is suppressed, blocking threat learning and reactivating the locus coeruleus-dependent neural circuitry supporting attachment learning [22,32]. The mechanism for maternal suppression of fear learning is through social buffering as determined by microdialysis of the hypothalamic paraventricular nucleus (PVN): that is, maternal presence reduces pups' basal corticosterone levels via reduction of NE release into the pup's PVN, resulting in blockade of HPA activation [58]. This link between PVN NE and amygdala-dependent threat behaviors has been shown to be causal: blockade of PVN NE prevents maternal social buffering of HPA activation. Furthermore, maternal social buffering of the HPA axis can be overridden by a microinjection of NE receptor agonists into the PVN, which increases corticosterone in the mother's presence and permits the amygdala-dependent behavioral response to threat. More recently, these findings have been paralleled in humans and non-human primates [5,7,59].

However, social buffering is compromised in children reared with an abusive caregiver [6]. This has been modeled in non-human primates reared with a naturally abusive caregiver [7]. Rodent research from our lab has modeled abusive caregiving using the Scarcity Model of low resources, where the mother is provided with insufficient nest-building material. This manipulation produces abnormal maternal behaviors, including increases in rough handling or trampling of pups as well as reduced nurturing behavior, even though pups gain weight normally [47]. Across species, these models have confirmed that early life trauma from the caregiver degrades the mother's ability to socially buffer both corticosterone levels and threat response behavior, suggesting loss of some beneficial effects of social buffering [5,6,60]. Furthermore, pups reared with a stressed mother exhibit enhanced levels of corticosterone, arising both from corticosterone delivered through the mother's milk and endogenously generated corticosterone release by the pup [61]. These increases in corticosterone induced by early-life abuse prematurely end the SHRP, resulting in a precocious termination of the sensitive period for attachment learning [62] (Figure 4). Thus early life trauma alters the neurobehavioral trajectory of threat response development.

Figure 4
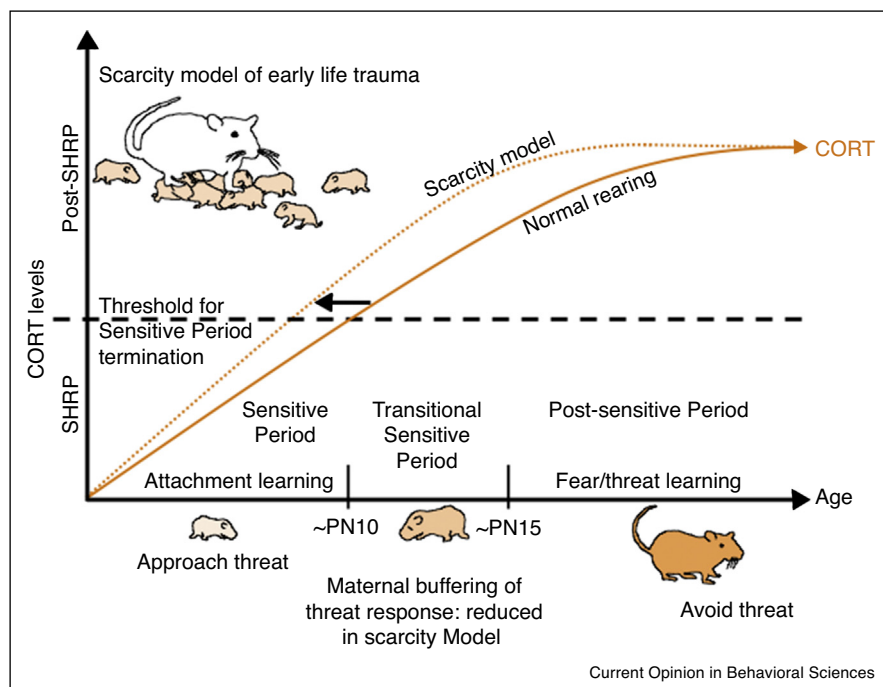
Early life abuse increases pup corticosterone and induces premature closure of the sensitive period for attachment learning. In the Scarcity Model of early life abuse, mother rats are provided with insufficient nesting material for five days of early post-natal development (PN8-12). In response, the mother is more likely to scatter, trample or roughly transport her pups. Notably, pup corticosterone levels increase more rapidly in response to the maltreatment, which triggers early (∼PN7) termination of the stress hyporesponsive period (SHRP), which is the sensitive period for attachment learning. Early onset of the Transitional Sensitive Period observed in the Scarcity Model is associated with reduced maternal buffering of pup corticosterone response to threat stimuli.

Social transmission of fear

However, complete suppression of fear in offspring is likely not adaptive in all situations and indeed, the mother is capable of overriding this social buffering suppression of fear. The mother is also capable of increasing pups' corticosterone and this highlights a critical role for social transmission of fear from the mother to infants [63,64]. Specifically, if the caregiver expresses fear of an odor in the presence of the pups, the pups will learn to fear that odor. The mechanism for this learning appears to be the mother's release of an alarm pheromone, which increases basal corticosterone level in pups and permits amygdala plasticity for fear learning of the odor. Thus, although the caregiver's presence at default buffers stress and fear, the presence of the frightened caregiver induces fear in pups. Similar social learning occurs throughout development and has been well documented in adults [65,66].

Conclusion

We reviewed the role of the stress hormone corticosterone with an emphasis on new directions in our understanding of how this stress hormone has immediate impact on pup adaptive behavior. Furthermore, while the negative effects of stress are typically emphasized, it is also clear that normal increases in corticosterone over development can produce adaptive behaviors in pups. Here we gave examples of how corticosterone in the pup is controlled by the mother for adaptive expression of fear: socially buffering pups' corticosterone to decrease fear but also increasing pups' corticosterone via caregiver's alarm pheromone to increase fear. The caregiver's control of pup behavior and learning enables the caregiver to regulate pups' expression of adaptive behaviors, ultimately benefiting pups' survival.

Conflicts of interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

We further confirm that any aspect of the work covered in this manuscript that has involved either experimental animals or human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript. We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). He/she is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs. We confirm that we have provided a current, correct email address which is accessible by the Corresponding Author and which has been configured to accept email from ans525@nyu.edu.

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- •• of outstanding interest

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