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Current Opinion in Behavioral Sciences

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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Current Opinion in Behavioral Sciences 2017, **14**:78–85

This review comes from a themed issue on **Stress and behavior**

Edited by **David A Morilak** and **Carmen Sandi**

http://dx.doi.org/10.1016/j.cobeha.2016.12.010

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].

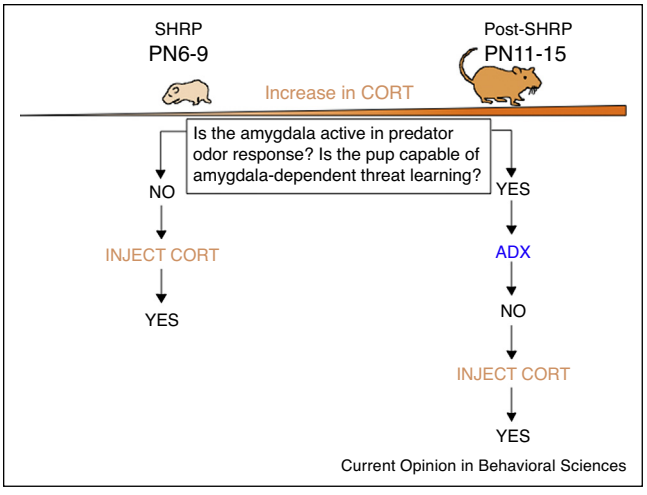
The stress hormone corticosterone is typically thought of as damaging to infant behavioral and neural development [8,9]. However, it is now clear that corticosterone is also critically important for normal brain development and normal infant neurobehavioral functioning [10,11]. Here we review the effects 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