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Behavioral effects of peripheral corticotropin-releasing factor during maternal separation may be mediated by proinflammatory activity

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Summary When guinea pig pups are separated from their mothers in a novel environment, an initial period of active behavior (vocalizing, locomotor activity) wanes after an hour or so and is replaced by a second, passive stage characterized by a crouched stance, closed eyes, and extensive piloerection. If pups are given a peripheral injection of 7–14 μg of corticotropin-releasing factor (CRF) prior to testing, the passive behaviors occur immediately upon separation. We found that intracerebroventricular infusion of 1–10 μg of CRF did not increase passive behavior relative to vehicle infusion, but that peripheral injection of the anti-inflammatory cytokine, interleukin-10, attenuated the passive behavior induced by peripheral CRF injection. These results together with previous findings suggest that peripheral CRF administration affects behavior of separated guinea pig pups through a mechanism that involves peripheral proinflammatory activity. The possible role of endogenous peripheral CRF in the behavioral response of untreated pups during maternal separation is considered.
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1. Introduction

It is well established that corticotropin-releasing factor (CRF) is a primary mediator of the body's diverse responses to stressors. CRF neurons in the CNS drive not only pituitary–adrenal activity, but also responses of sympathetic, locus coeruleus/noradrenergic, and gastrointestinal systems (Dunn and Berridge, 1990; Owens and Nemeroff, 1991). Central CRF activity also appears to underlie widespread behavioral effects associated with stress or anxiety in laboratory animals, including emergence into, and activity in, an open field (Takahashi et al., 1989), activity on an elevated plus maze (Heinrichs et al., 1992; Skutella et al., 1994), shock-induced freezing (Swiergiel et al., 1993), conditioned defeat (Jasnow

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et al., 1999), appetite suppression (Krahn et al., 1986), and the ultrasonic vocalization response of rat pups to maternal separation (Harvey and Hennessy, 1995; Insel and Harbaugh, 1989). CRF also appears to be widely distributed in the periphery, including the gastrointestinal tract, pancreas, liver, lungs, reproductive organs, placenta, immune system, skin, sympathetic ganglia, and adrenal medulla (Dufau et al., 1993; Emeric-Sauval, 1986; Krukoff, 1986; Nazarloo et al., 2006). In the periphery, CRF and the closely related urocortins influence a range of functions including gastrointestinal motility (Stengel and Tache', 2009), inflammation (Karalis et al., 1997; Paschos et al., 2009), and reproductive (Dufau et al., 1993) and cardiovascular (Coste et al., 2002) activity. Peripheral CRF activity, like CRF in the CNS, may be an important mediator of stress responses. CRF is co-released with catecholamines from the adrenal medulla following hemorrhage or splanchnic nerve stimulation (Bruhn et al., 1987; Edwards and Jones, 1988) and peripheral CRF signaling plays a key role in stress-related gastrointestinal disorders, notably inflammatory conditions (Paschos et al., 2009; Stengel and Tache', 2009; Zheng et al., 2009).

Although CRF is unlikely to cross the blood–brain barrier into the brain (Banks and Kastin, 1985; Martins et al., 1996), peripherally administered CRF occasionally has been found to produce behavioral effects. In one study, a subcutaneous (SC) injection of a dose of CRF that had no impact on circulating glucocorticoid levels facilitated retention of passive avoidance learning in rats (Veldhuis and De Wied, 1984). In another, intracardial CRF reduced rats' tail flick response to heat (Ayesta and Nikolarakis, 1989). Peripheral injection of CRF also markedly affects the behavior of preweaning guinea pigs. When injected SC with 7–14 μg of CRF and isolated in a novel cage, pups showed a dramatic reduction in the vocalizing and locomotor activity that is characteristic of the immediate reaction to the separation procedure (Hennessy et al., 1991). This response suppression could not be duplicated with injection of ACTH, nor reversed with naloxone (Hennessy et al., 1991), suggesting that it was not mediated by other hormones of the HPA axis. Further, the behavior suppression did not appear to be the result of emission of incompatible behaviors, including stress-induced "freezing" (Becker and Hennessy, 1993), nor did it appear due to motor incapacity (Becker and Hennessy, 1993), or CRF-induced hypotension (Hennessy et al., 1995). The effect of CRF injection was blocked by peripheral administration of a peptide CRF-receptor antagonist (Hennessy et al., 1995), indicating that it was mediated by CRF receptors.

At about this time we also noted that CRF induced a distinct passive behavioral reaction during the inhibition of active behavior (Becker and Hennessy, 1993). Specifically, pups adopted a characteristic crouched posture; their eyes were often closed, and they exhibited extensive piloerection. Our interest in the passive response increased as a result of two additional results. First, it was found that pups displayed this passive behavior not only immediately following separation when injected with CRF, but also during more-prolonged periods of separation (>1 h) under non-drug conditions (Hennessy et al., 1995). Second, pups injected peripherally with a non-specific, peptide CRF-receptor antagonist exhibited an increase in active behavior, and fewer pups exhibited any passive behavior, during a 1-h test (McInturf and Hennessy, 1996). Because the peptide antagonist was unlikely to cross the blood–brain barrier, this finding suggested that endogenous peripheral CRF might be part of the mechanism that normally shifts pups from an initial active, to a subsequent passive, phase of behavioral response during separation.

Additional study of the passive behavior during prolonged separation under non-drug conditions indicated that proinflammatory factors contributed to the response. Specifically, it was found that: (1) direct activation of a proinflammatory response produced the passive response immediately following separation, much as did CRF injection (Hennessy et al., 2004); (2) any of three anti-inflammatory agents reduced the passive behavior during prolonged (3-h) separation (Hennessy et al., 2007b; Perkeybile et al., 2009; Schiml-Webb et al., 2006); (3) an increase in the expression of the proinflammatory cytokine, tumor necrosis-α, was observed in spleen over the course of a 3-h separation (Hennessy et al., 2007a). These results, together with findings indicating that CRF in the periphery has various proinflammatory effects (e.g., Ilias and Mastorakos, 2003; Karalis et al., 1997; Paschos et al., 2009), raised the possibility that CRF injection induced passive behavior through a proinflammatory mechanism. Peripheral proinflammatory activity can induce central proinflammatory activity through various pathways (Quan and Banks, 2007). Central proinflammatory activity, in turn, is known to produce behavioral changes characterized by inactivity and reduced engagement with the environment (Dantzer et al., 2008). We then found that administration of α-melanocyte stimulating hormone (α-MSH)—a peptide with broad anti-inflammatory effects (Catania and Lipton, 1993; Lipton and Catania, 1997)—significantly reduced passive behavior of guinea pig pups injected with CRF (Schiml-Webb et al., 2009). While these findings implicated a proinflammatory mechanism for CRF's effect, α-MSH is known to have a variety of other physiological actions (Gonzalez et al., 1996; Panksepp and Abbott, 1990; Rao et al., 2003), leaving open alternative interpretations.

The primary purpose of the present experiments was to examine the means by which peripheral CRF administration induced the passive behavior response in separated guinea pig pups. Experiment 1 evaluated the effect of intracerebroventricular (ICV) infusion of CRF on behavior during separation. If peripherally administered CRF crosses into the brain to induce passive behavior, ICV CRF might also be expected to induce passive behavior. Experiment 2 provided a second test of the hypothesis that peripheral CRF acts through a proinflammatory mechanism. The ability of a peripheral injection of interleukin-10 (IL-10) to attenuate the behavioral effect of SC CRF injection was assessed. IL-10 is a cytokine with potent anti-inflammatory actions. It has been found to reduce the behavioral response to proinflammatory activation produced by injection of lipopolysacchride (Bluthé et al., 1999; Nava et al., 1997). Further, Perkeybile et al. (2009) recently found central IL-10 to blunt the passive behavior of guinea pig pups during prolonged separation under non-drug conditions.

2. Method

2.1. Subjects

Albino guinea pigs (*Cavia porcellus*) were bred in our laboratory. Each mother and her litter were housed in opaque plastic cages (73 cm × 54 cm × 24 cm) with wire fronts and

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