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Research report

Timecourse and corticosterone sensitivity of the brain, pituitary, and serum interleukin-1β protein response to acute stress

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Abstract

Activation of peripheral immune cells leads to increases of interleukin-1β (IL-1β) mRNA, immunoreactivity, and protein levels in brain and pituitary. Furthermore, IL-1β in brain plays a role in mediating many of the behavioral, physiological, and endocrine adjustments induced by immune activation. A similarity between the consequences of immune activation and exposure to stressors has often been noted, but the potential relationship between stress and brain IL-1β has received very little attention. A prior report indicated that exposure to inescapable tailshocks (IS) raised levels of brain IL-1β protein 2 h after IS, but only in adrenalectomized (and basal corticosterone replaced) subjects. The studies reported here explore this issue in more detail. A more careful examination revealed that IL-1β protein levels in hypothalamus were elevated by IS in intact subjects, although adrenalectomy, ADX (with basal corticosterone replacement) exaggerated this effect. IL-1β protein increases were already present immediately after the stress session, both in the hypothalamus and in other brain regions in adrenalectomized subjects, and no longer present 24 h later. Furthermore, IS elevated levels of IL-1β protein in the pituitary, and did so in both intact and adrenalectomized subjects. IS also produced increased blood levels of IL-1β, but only in adrenalectomized subjects. Finally, the administration of corticosterone in an amount that led to blood levels in adrenalectomized subjects that match those produced by IS, inhibited the IS-induced rise in IL-1β in hypothalamus and pituitary, but not in other brain regions or blood.

Keywords: Interleukin-1β; Stress; Brain; Pituitary; Serum; Glucocorticoid

1. Introduction

Interleukin-1β (IL-1β) is a cytokine that is produced in the periphery by a variety of cell types and plays a number of roles in immune and inflammatory processes [8]. IL-1β and the other members of the IL-1 family (IL-1α, the prohormone for IL-1, IL-1 converting enzyme, IL-1 accessory protein, IL-1 receptor antagonist, and IL-1 receptors and their fragments) have also been localized in the brain. IL-1β in brain is activated by neural injury [33], but IL-1β mRNA [5], bioactivity [32], immunoreactivity [44] and protein levels [28] are also increased in brain following the activation of peripheral immune cells by viral and bacterial products such as lipopolysaccharide (LPS). Furthermore, brain IL-1β participates in the mediation of many of the behavioral and physiological responses to peripheral infection and immune activation [see Ref. [6], for review, Ref. [21]]. Thus, intracerebroventricular (ICV) administration of IL-1β produces many of the same alterations as are produced by infectious agents, and the ICV and regional injection of the IL-1 receptor antagonist (IL-1ra) blocks or attenuates many of the brain-mediated consequences of peripheral immune activation [see Ref. [22] for review]. The fact that IL-1β manufactured in brain is involved in mediating aspects of the host response to peripheral infection is sensible because IL-1β from the periphery crosses into the brain in only very small amounts [4].

A similarity between the neural, behavioral, and physiological consequences of exposure to environmental stressors and to immune-activating agents has often been noted [10]. This similarity suggests a possible role for brain IL-1β in mediating the sequelae of exposure to stressors. However, very little research has been directed at an exploration of the relationship between environmental stressors and brain IL-1β. Central administration of IL-1ra

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has been reported to block the brain monoamine and pituitary-adrenal response to immobilization [37], and the potentiation of fear conditioning and interference with escape learning produced by a session of inescapable tailshock (IS) [20]. With regard to the induction of IL-1β in brain by stressors, Minami et al. [23] found an increase in IL-1β mRNA in hypothalamus produced by immobilization, while we [28] have found an increase in IL-1β protein levels in a number of brain regions 2 h after IS. However, the increase in IL-1β protein was only demonstrable in adrenalectomized subjects.

It is to be expected that adrenalectomy (ADX) would enhance IL-1β produced by stressors. This is because stressors increase adrenal glucocorticoid (corticosterone (CORT) in the rat) levels, and CORT inhibits IL-1β gene transcription [19], destabilizes IL-1β mRNA [1], and inhibits a number of translational and post-translational processes [16] that are involved in IL-1β production. Unfortunately, the absence of any IL-1β increase in intact subjects rendered the functional significance of stress-IL-1 relationships difficult to assess. However, in subsequent work that used a more sensitive ELISA to detect IL-1β protein we have consistently observed an increase in IL-1β protein levels in hypothalamus of intact subjects after IS. Here we further explore this issue more thoroughly, as well as add further timepoints after stress (the prior report measured IL-1 only 2 h after IS) and other tissues (pituitary and serum) to an examination of stress-IL-1 relationships. Basal CORT was replaced in ADX subjects in these and in prior experiments. This is because the intent was to remove the CORT increase produced during and shortly after IS, not basal levels of CORT. The argument is that it is the CORT rise produced by IS that is critical, and so the rationale is to remove only the rise from basal levels, not the basal levels themselves. In addition, ADX removes more than the CORT rise to IS, but the increase in other adrenal products as well. Thus, we also examine whether CORT is the critical IL-1β inhibitory substance removed by ADX.

2. Materials and methods

2.1. Subjects

Male pathogen-free Sprague–Dawley rats (350–400 g; Harlan, Indianapolis, IN) were single housed in hanging metal cages at 25 ± 2°C with a 12 h light/dark cycle (lights on at 0600 h). Subjects were acclimated to the colony for 14 days before experimentation began. Standard rat chow and water were freely available. Care and use of animals were in accordance with the University of Colorado Institutional Animal Care and Use Committee.

2.2. Adrenalectomy

Bilateral adrenalectomies were aseptically performed under halothane anesthesia (Halocarbon Laboratories, River Edge, NJ). All removed tissue was examined immediately to ensure complete removal of the adrenal gland. Sham operated animals received the identical procedure, except that the adrenal glands were gently manipulated with forceps but not removed. Steroid replacement began for ADX animals immediately after surgery. ADX animals received corticosterone (CORT) replacement in their drinking water since this method has been shown to mimic the normal circadian pattern of CORT secretion [14]. CORT (Sigma, St. Louis, MO) was initially dissolved in ethyl alcohol (EtOH) and diluted to a final concentration of 25 μg/ml in 0.2% EtOH. CORT–water also contained 0.5% saline. Sham animals received drinking water containing 0.2% EtOH. Animals were allowed 6 weeks to recover before any experiments were performed.

2.3. Inescapable tailshock treatment

All rats were handled and weighed 2 days before each study began. Animals either remained undisturbed in their home cages as controls (HCC) or were exposed to IS. The stress protocol involved placing the rats in a Plexiglas restraining tube (23.4 cm long and 7 cm in diameter) and exposing them to 100, 5-s 1.6 mA inescapable shocks, with an average intertrial interval of 60 s. The shocks were applied through electrodes taped to the tail. The animals were stressed between 0800 and 1000 h, and after stressor termination were returned to their home cages.

2.4. Exogenous CORT treatment

CORT (Sigma, St. Louis, MO) was injected subcutaneously in ADX subjects at a dose of 2.5 mg/kg dissolved in propylene glycol (Sigma, St. Louis, MO) immediately prior to IS exposure. The rationale was to produce a plasma CORT profile similar to that produced by IS in intact subjects. This dose of CORT administered to ADX subjects has been previously shown to produce a time-course of plasma CORT very similar to that produced in intact subjects exposed to IS identical to that used here [11]. Control injections were equivolume propylene glycol, with all injections given between 0730 and 0800 h.

2.5. Tissue and blood collection

Animals were anesthetized with a brief exposure to ether and brains were quickly removed following decapitation. All dissections were performed on an ice-cold frosted glass plate and tissues were quickly frozen on dry ice. Tissue samples, which included hypothalamus, hippocampus, nucleus tractus solitarius (NTS)/area postrema (AP), frontal cortex, posterior cortex, cerebellum, and pituitary were stored at -70°C until the time of sonication. Trunk blood was collected by decapitation.

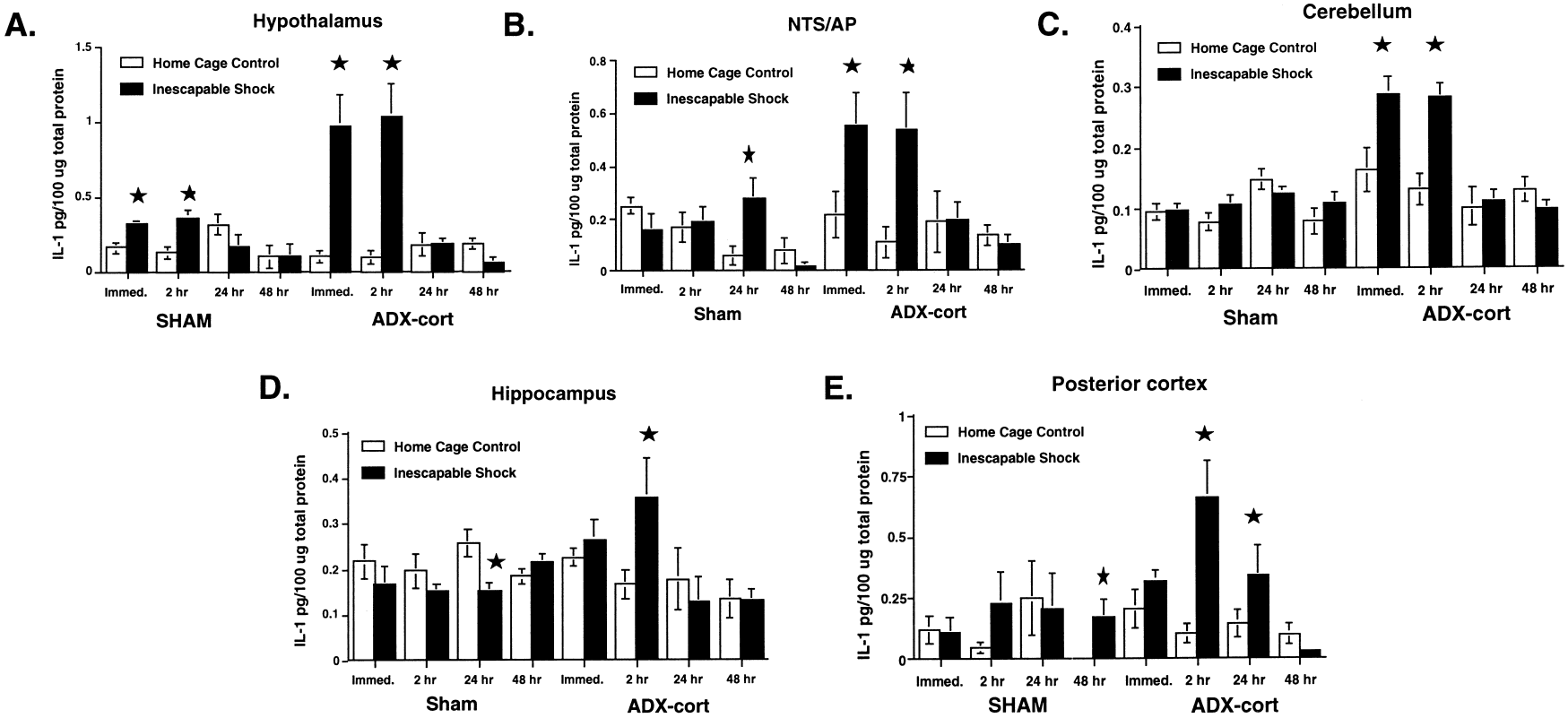

Fig. 1. Levels of IL-1 protein in the hypothalamus (A), nucleus tractus solitarius (B), cerebellum (C), hippocampus (D), and posterior cortex (E) of sham and ADX-CORT replaced rats immediately, 2, 24, and 48 h following inescapable shock (black bars) or home cage control (white bars) treatment. A Star indicates that the IS group differs reliably from its control.

2.6. Tissue and blood processing

Each tissue was added to 0.25–0.5 ml of Iscove's culture medium containing 5% fetal calf serum and a cocktail enzyme inhibitor (100 mM amino-*n*-caproic acid, 10 mM EDTA, 5 mM benzamidine HCl, and 0.2 mM phenylmethyl sulfonyl fluoride). Total protein was mechanically dissociated from tissue using an ultrasonic cell disrupter (Fisher Scientific, Pittsburgh, PA). Sonication consisted of 10-s of cell disruption at setting #10. Sonicated samples were centrifuged at $10{,}000 \times g$, at 4°C, for 10 min. Supernatants were removed and stored at 4°C until ELISA was performed. Bradford protein assays were also performed to determine total protein concentrations in sonication samples. Serum was separated from whole blood by centrifugation and samples were stored at -20°C until time of assay.

2.7. IL-1β protein quantitation

Levels of IL-1β protein were determined using a commercially available rat IL-1β ELISA kit (R&D Systems, Minneapolis, MN) as previously described [28]. The assay was performed according to the manufacturer's instructions. 50 μl of either serum or tissue sonicates were used for the assay. This ELISA kit utilizes a goat anti-rat IL-1β polyclonal antibody that can recognize both recombinant (r), as well as natural rat IL-1β. No significant cross-reactivity was observed with this antibody to rHuman IL-1 receptor type I, rHuman IL-1 receptor type II, rHuman IL-1 receptor antagonist, rRat IL-1α, rRat IL-2, rRat IL-4, rRat Interferon-α, rRat Tumor necrosis factor-α, rMouse IL-1α or rMouse IL-1 receptor antagonist, according to manufacturers data. The detection limit of the assay is 5 pg/ml according to manufacturer's data. However, we have found the limit to be closer to 10 pg/ml. Taking the total amount of protein in each sample into account, the concentration of IL-1β protein in the samples is presented as pg of IL-1β/100 g of total protein. The intra- and inter-assay coefficients of variance have been found to be $< 10\%$. We have also determined the recovery of rRat IL-1β protein from sonicated brain tissue samples and found it to be between 50–70%. This was assessed by adding a known concentration of rRat IL-1β into brain samples prior to sonication. The tissues were processed as previously described and the ELISA was performed. The recovered values were compared to the values of brain samples without the addition of rRat IL-1 to determine the percentage of recovery.

2.8. Experimental design

In the first experiment ADX and Sham subjects received either IS or remained in their home cages. Separate IS groups were sacrificed either immediately after the session, 2, 24, or 48 h later as described above. Controls were sacrificed at the exact same times. It is necessary to have separate controls sacrificed along with each of the IS groups, even though the immediate, 24, and 48 h groups are tested at the same time of day, because IL-1β levels can vary with colony conditions. Thus, the design was a $2 \times 2 \times 4$ factorial, with 6–8 subjects per group. Tissue and blood were collected as described above. In the second experiment ADX rats received either a 1 mg/kg injection of CORT or vehicle before a session of IS or home cage control treatment. Sacrifice occurred 2 h after the session. Thus, the design was a 2×2 factorial.

2.9. Statistical analysis

Data were analyzed by either ANOVA or repeated measures ANOVA where appropriate, and post hoc Fishers PLSD tests set at $\alpha = 0.05$.

3. Results

3.1. Brain Il-1β

Fig. 1 shows IL-1 protein levels in the brain regions examined after IS and Home Cage control treatment in ADX and Sham operated rats. An overall ANOVA includ-

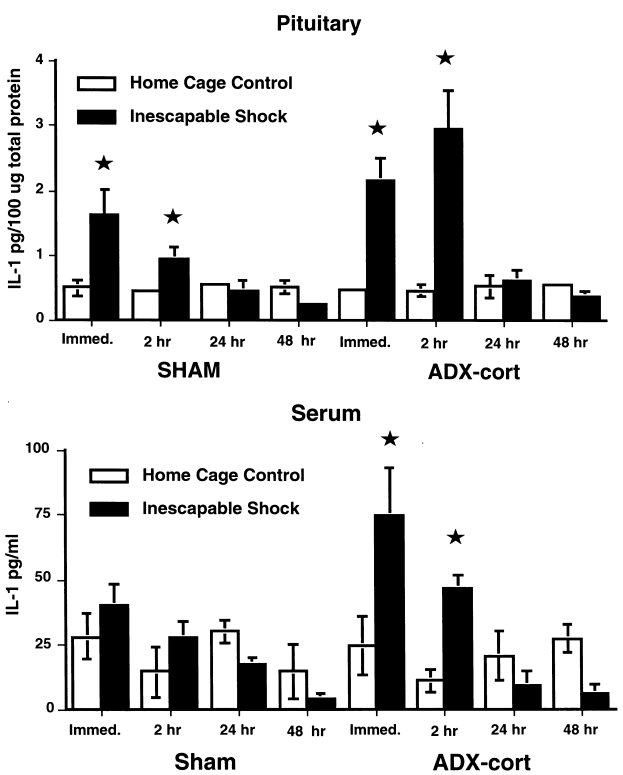

Fig. 2. Levels of IL-1 protein in the pituitary gland (A) and serum (B) of sham and ADX-CORT replaced rats immediately, 2, 24, and 48 h following inescapable shock (black bars) or home cage control (white bars) treatment. A Star indicates that the IS group differs reliably from its control.

ing all brain regions yielded a significant IS × ADX × Time × Regions interaction [$F(15,360) = 2.898$; $p < 0.0005$]. In addition, main effects of ADX [$F(5,360) = 24.071$; $p < 0.0001$] and IS [$F(5,360) = 6.003$; $p < 0.0001$] were observed.

The overall ANOVA justifies examination of each region separately. With regard to the hypothalamus, IL-1β levels were indeed elevated immediately and 2 h after IS in Sham subjects, an effect exaggerated by ADX. IL-1β levels were no longer elevated 24 or 48 h after IS. There was a significant IS × ADX × time interaction [$F(3,72) = 5.222$; $p < 0.005$]. A main effect of IS was observed, indicating that IS increased IL-1β levels [$F(1,72) = 27.905$; $p < 0.0001$]. In addition, reliable main effects of ADX [$F(1,72) = 10.090$; $p < 0.005$] and Time [$F(3,72) = 9.512$; $p < 0.0001$] were also observed. Post-hoc analyses revealed a significant increase in IL-1β levels immediately and 2 h after IS in both sham and ADX subjects in response to IS.

IL-1β levels in the NTS/AP did not vary consistently in Sham subjects, but large increases in IL-1β were produced by IS in ADX subjects at the immediate and 2 h timepoints. There was a significant IS × ADX × Time interaction [$F(3,72) = 4.432$; $p < 0.01$]. Reliable main effects of IS [$F(1,72) = 7.859$; $p < 0.01$], ADX [$F(1,72) = 7.854$; $p < 0.01$] and Time [$F(3,72) = 6.006$; $p < 0.005$] were also observed. Post-hoc analyses revealed a significant increase in IL-1β levels at the immediate and 2 h timepoints in ADX subjects in response to IS. In addition, there was a reliable difference in IL-1β levels 24 h after IS in Sham subjects.

The cerebellum revealed a pattern similar to that observed in the NTS/AP–no IS-induced increase in Shams, but large increases immediately and 2 h after IS in ADX subjects. There was a significant IS × ADX × Time interaction [$F(3,72) = 3.963$; $p < 0.05$], and reliable main effects of IS [$F(1,72) = 11.273$; $p < 0.005$], ADX [$F(1,72) = 28.941$; $p < 0.0001$] and Time [$F(3,72) = 5.831$; $p < 0.005$]. Again, post-hoc analyses revealed a significant increase in IL-1β levels at immediate and 2 h timepoints after IS only in ADX subjects.

The pattern in hippocampus was slightly different. There were no increases produced by IS in Shams, but IL-1β increases occurred in ADX subjects only 2 h after IS, and not immediately. The IS × ADX × Time interaction was not significant [$F(3,72) = 1.901$; $p > 0.05$]. However, there were reliable IS × ADX [$F(1,72) = 4.617$; $p < 0.05$] and ADX × Time [$F(3,72) = 3.462$; $p < 0.05$] interactions.

The pattern in the posterior cortex was quite similar to the hippocampus. The only reliable effect was the IS × Time interaction [$F(3,72) = 3.275$; $p < 0.05$].

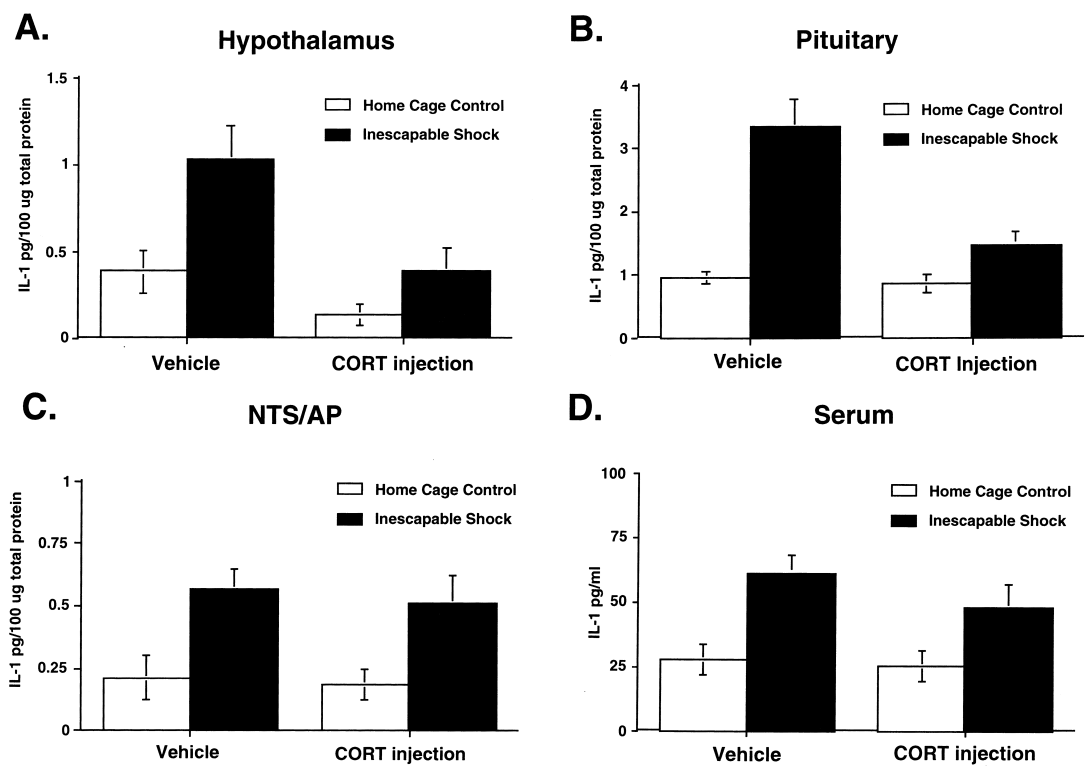

Fig. 3. Levels of IL-1 protein 2 h after inescapable shock (black bars) or after home cage control treatment (white bars) in the hypothalamus (A), pituitary (B), nucleus tractus solitarius (C), and serum (D) of ADX-CORT replaced rats receiving either a subcutaneous injection of vehicle or CORT before treatment. These data include home cage controls (white bars) and IS-treated rats (black bars). Each group contains nine subjects.

3.2. 3.2 Serum and pituitary IL-1β

Serum and pituitary levels of IL-1β are shown in Fig. 2. Pituitary IL-1β followed much the same pattern as did hypothalamic IL-1β, with increases in Sham subjects immediately and 2 h after IS, and ADX exaggerating these increases. There was a reliable IS × ADX × Time interaction [$F(3,72) = 3.879$; $p < 0.05$], and reliable main effects of IS [$F(1,72) = 34.934$; $p < 0.0001$], ADX [$F(1,72) = 10.074$; $p < 0.005$], and Time [$F(1,72) = 13.609$; $p < 0.0001$]. Post-hoc analyses revealed a significant increase in IL-1β levels immediately and 2 h after IS in both sham and ADX subjects. In serum there was a elevation produced by IS only in ADX animals immediately and 2 h after IS. There was a reliable IS × Time interaction [$F(3,72) = 7.936$; $p < 0.005$], but a significant IS × ADX × Time interaction was not observed [$F(3,72) = 1.623$; $p > 0.05$]. Post hoc analyses revealed reliable IS-induced increases immediately and 2 h after IS in ADX subjects. The differences in Shams did not approach significance.

3.3. CORT administration

The effects of administering CORT before IS in ADX subjects are shown in Fig. 3. Only hypothalamus, NTS/AP, pituitary, and serum were assessed. CORT suppressed the IL-1β increase produced by IS in the hypothalamus and pituitary, but did not do so in the NTS/AP and serum. For the hypothalamus, there was a reliable main effect of CORT [$F(1,32) = 10.976$; $p < 0.005$], IS [$F(1,32) = 10.997$; $p < 0.005$], and their interaction [$F(1, 32) = 5.78$, $p < 0.01$]. For pituitary there was a reliable interaction between CORT and IS [$F(1,32) = 12.067$, $p < 0.005$], as well as a main effect of CORT [$F(1,32) = 14.629$, $p < 0.001$] and IS [$F(1,32) = 33.913$, $p < 0.0001$]. However, in the NTS/AP and serum, IS increased IL-1β protein levels [$F(1,32) = 15.519$, $p < 0.0005$] and [$F(1,32) = 16.322$, $p < 0.0005$], but CORT had no effects [$F(1,32) = 0.246$, $p > 0.05$] and [$F(1,32) = 1.330$, $p > 0.05$].

4. Discussion

The present experiments confirm the finding reported by Nguyen et al. [28] that IL-1β protein levels in hypothalamus, NTS/AP, cerebellum, hippocampus, and posterior cortex are elevated 2 h after IS in ADX basal CORT replaced animals. The experiments add the new findings that (a) IL-1β levels are increased by IS in hypothalamus in intact subjects, (b) IL-1β increases are already present immediately after IS and do not require 2 h after IS to develop, (c) IL-1β increases are no longer present 24 h after IS, (d) IS increases IL-1β in serum in ADX basal CORT replaced subjects, (e) IL-1β protein levels are elevated in pituitary after IS in sham subjects, and this increase is potentiated by ADX plus basal CORT replacement, (f) CORT injection that produces blood levels of CORT similar to that produced by IS inhibit the IL-1β increase produced by IS in hypothalamus and pituitary, but not in NTS/AP and blood.

Perhaps the most important aspect of these findings is that IS-induced elevation of IL-1β protein levels are observable in hypothalamus and pituitary in non-ADX subjects. This is important because a functional role for IL-1β in mediating stress effects requires that increases in IL-1β be demonstrable in intact subjects. It should be stated again that we have observed this increase in hypothalamus in other experiments, and so we are confident that it is a reliable result. Although the increase in intact subjects in hypothalamus was relatively small compared to that which occurred in ADX basal CORT replaced subjects, it nevertheless represented a two to three-fold increase over control levels. Furthermore, even small differences in IL-1β activity can have important outcomes. IL-1β is an extremely potent molecule, with very little receptor occupancy being required for biological signaling. Indeed, it has been estimated that only 10 receptors must be occupied to induce cellular activation [9], and microinjection into the hypothalamus of as little as 1.0 pg can have behavioral effects [29]. It is also of note that IL-1β brain microinjection studies have overwhelmingly focused on the hypothalamus as an active site. Intra-hypothalamic microinjection of pg to ng quantities of IL-1β have produced noradrenergic, dopaminergic, and serotonergic activation [36], reduced activity and sexual behavior [3], inhibited gastric acid secretion [34], sleep alterations [38], reductions in food and water intake [15], increases in blood pressure and heart rate [27], a peripheral acute phase response [25], changes in pain sensitivity [29], fever [35], and leukocytosis [26]. Interestingly, stressors such as IS produce many of these outcomes including the peripheral changes such as leukocytosis and acute phase responses [7]. The fact that IL-1β increases occurred in other brain regions in ADX subjects suggests that IS produces a drive to IL-1β producing cells in these regions, but that a stress-responsive product of the adrenals inhibits IL-1β protein expression. It may be that IL-1β does increase in these regions, but that the increases are either quite localized or not detectable with the procedures used here. Thus, a role for IL-1β in other regions cannot be discounted.

It is also of interest that IS produced an increase in the pituitary content of IL-1β. Stressor-induced increases in pituitary IL-1β have not previously been reported. Thus, this finding provides another instance of similarity in the effects of peripheral immune activation and stress, since the intraperitoneal and intravenous administration of LPS increases pituitary cell expression of IL-1β mRNA [18] and IL-1β immunoreactivity [40]. LPS has been suggested to increase pituitary IL-1β via a direct action on the pituitary [46], but this is not possible for IS. Corticotropin releasing hormone (CRH) increases the density of IL-1 receptors in the pituitary [41], but its effects on pituitary

IL-1β are not known. The role of IL-1β in the pituitary in mediating stress responses is unknown. However, it has been suggested that IL-1β in the pituitary has paracrine and autocrine functions [2], and pituitary IL-1 may participate in the regulation of ACTH release to stressors [30]. In addition, IL-1β stimulates IL-6 release from pituitary cells [39], and stressors increase the levels of IL-6 in blood [48]. Thus, pituitary IL-1 may play a regulatory role in stress-endocrine interactions.

The rapidity with which increases in IL-1β protein levels were observed also deserves comment. IL-1β protein was elevated when examined immediately after the stressor session. Interpretation is somewhat difficult because the stressor session was roughly 2 h in duration, but prior pilot work has indicated that a small number of ISs do not increase IL-1β protein levels. However, we have also found rapid increases in IL-1β protein levels in brain following LPS injection (unpublished data), within 30 min or less following administration. This increase is likely to have occurred too quickly to represent newly synthesized IL-1β, and may represent rapid post-translational processing of constitutive pro-IL-1β. IL-1β is synthesized as a 33 kDa precursor (pro-IL-1β) that is biologically inactive, with mature 17.5 kDa IL-1β formed from pro-IL-1β by proteolytic cleavage by the IL-1 converting enzyme (ICE) [see Ref. [45], for a review of IL-1 processing]. The active forms of ICE also result from proteolytic cleavage of a precursor, and stimulation by LPS produces the rapid processing of ICE [47] and leads to an increase of ICE mRNA in both the pituitary and the hypothalamus [42]. Mature IL-1β can be produced from pro-IL-1β by ICE action in less than 7.5 min [13]. Furthermore, there is evidence that the brain does store pre-formed pro-IL-β in a constitutive fashion [43], and so the early increase in IL-1β after LPS administration may derive from the cleavage of pre-existing pro-IL-β by ICE [22]. It is possible that the increase in brain IL-1β levels observed in the present studies also derives from the processing of preformed pro-IL-1β. It is intriguing that adenosine triphosphate (ATP) induces increases in ICE activity within minutes [13], since IS has been shown to increase ATP in brain [24]. It can also be noted that ADX increases ICE mRNA [17]. It may be that prevention of the CORT rise from basal levels normally produced by IS inhibits ICE, providing a potential mechanism for the potentiation of IL-1β protein increases produced by ADX. Thus it is possible that IS induces elevations in ATP leading to increases in ICE activity. The increase in ICE activity could very quickly lead to elevations in IL-1β protein by cleaving pro-IL-β.

The final issue concerns the role of CORT. Clearly, ADX combined with basal CORT replacement strongly potentiated the IL-1β increase produced by IS. This provides another parallel between stressor exposure and LPS, as ADX plus basal replacement also exaggerates the increase in IL-1β mRNA in brain produced by LPS [12]. Glucocorticoids inhibit many aspects of IL-1β processing-gene transcription [19], mRNA stability [1], translational processes [16], and post-translational processes [17]. Thus, the presumption has been that ADX potentiates IL-1β activity following immune activation such as that provided by LPS because ADX eliminates the CORT response to LPS above basal levels. This would suggest that the administration of CORT before IS to ADX subjects, at a dose known to produce the same profile of serum CORT over time as that produced by IS, should have returned IL-1β production to levels observed in intact subjects. This was the case for IL-1β in hypothalamus and pituitary, but not for NTS/AP and serum. The lack of effect of CORT in NTS/AP and serum cannot be explained by positing aberrant CORT receptor function due to ADX since basal CORT replacement was employed. The present data do not suggest an explanation, although it can be noted that CORT receptor densities are high in hypothalamus and pituitary. However, the data do suggest that an adrenal product other than CORT may be involved.

The suppressive effects of CORT and perhaps other adrenal products on IL-1β production suggests the possibility that stress-induced brain IL-1β increases may actually be more readily observed following weaker stressors than IS. IS produces a very rapid, large, and quite prolonged CORT response [11]. Indeed, CORT levels are maintained at well over 40 μg/dl for the entire 2 h session, and do not return to basal levels for 1–2 h after the session. It is therefore noteworthy that Pugh et al. [31] have found that 4 h of social isolation (placing a rat that is accustomed to group housing into an individual cage) produces large increases in brain IL-1β protein levels in a number of non-hypothalamic regions in intact rats. Social isolation produces a smaller and briefer rise in CORT than does IS (unpublished observations). Taken together, the data suggest that IL-1β in brain may play a role in mediating the sequelae of stressors, just as brain IL-1β is involved in mediating the neural and behavioral outcomes of infection.

Acknowledgements

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