Chapter 6

Understanding the Causes of Reduced Startle Reactivity in Stress-Related Mental Disorders

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/53066

1. Introduction

Many questions have plagued the study of the etiology and subsequent treatment of mental illness. In part, it is simply because, as far as we know, some mental illnesses are somewhat unique to the human condition. Moreover, clinical studies have produced many different results concerning potential biomarkers for conditions such as post-traumatic stress disorder (PTSD) and major depressive disorder (MDD). In this chapter, we review how we approached modeling a specific behavioral condition, suppression of the startle reflex, by examining whether one of two commonly associated peripheral biomarkers of anxiety and depression could potentially cause this rather specific symptom. The two peripheral systems under investigation were the hypothalamic-pituitary-adrenal (HPA) axis and the peripheral pro-inflammatory immune response, both of which have been implicated as a vulnerability factor, causal factor, or resultant (perpetuating) effect of PTSD and MDD.

Our general theory is that peripheral endocrine and immune signals, measured to be abnormal in patients with either PTSD or MDD (as well as other mental disorders), are actually perpetuating the behavioral features of these disorders. At the same time, if an individual has an immunosensitivity or has an overactive adrenal gland, s/he would be more likely to experience some of the symptoms associated with one of the particular mental illnesses. This may then lead the brain to compensate for those peripheral abnormalities, but, at the same time, cause other imbalances, which lead to the experience of a decline into mental illness. Thus, treating these peripheral markers as part of the "mental" disorder may be quite beneficial in normalizing certain aspects of the diagnosed abnormal behavior.

2. The startle reflex and mental health

2.1. The startle reflex as an assessment tool

One of the major impediments to the mechanistic study of mental illness is establishing analogs of the abnormal behaviors expressed in humans in animal models, especially in sub-primate species. This has led some to adopt reflex-based measures such that the face and construct validity of the behavior change can be readily translated between the model and patient populations. Consequently, a popular measures for the study of anxiety disorders has been the potentiation of the startle reflex; however, there is growing evidence that a dampening of the startle response may be indicative of changes in physiology that underlie different mental disorders.

The startle reflex comprises a 3-synaptic sensory-motor neuronal pathway that serves as a defensive behavioral response to abrupt, usually intense, stimuli. The acoustic startle response (ASR) is the most commonly used form for studying this reflex. As shown in Figure 1, the primary ASR circuit begins with neurons in the cochlear nerve, transmitting the representation of the acoustic stimulus from the cochlea of the inner ear to the cochlear nucleus (in the brainstem). Efferent pathways from the cochlear nucleus project to the nucleus reticularis pontis caudalis (PnC), in the pons, forming the second synapse in this reflex arc. The third synapse forms from the efferent projections from the PnC to various motor nuclei, through the recticulospinal spinal tracts to the muscles of the torso [1] and the muscles enervated by the facial nerve. These muscle enervations create a rapid cascade of near-immediate behavioral responses to abrupt acoustic stimuli, ranging from less than 10 ms to approximately 50 ms.

The ASR is modulated by several afferent connections originating from higher brain areas (midbrain, limbic, and cortical nuclei). At the level of the PnC, there are several inputs that can either enhance or inhibit the magnitude of an elicited ASR. In the area of fear and anxiety, the central amygdala and bed nucleus of the stria terminalis (BNST) are considered the 2 major excitatory modulation structures on this reflex [2]. Some have proposed that the BNST is the origin of anxiety-like behaviors whereas the nuclei of the amygdala are the origin of acute fear responses and explicit fear-learning [3, 4]. The amygdala is predominately associated with causing classically conditioned fear-potentiated ASRs [5], and, in fact, has been specifically shown not to have a role in startle inhibition, at least via a learned conditioned inhibitor [6]. On the other hand, the process known as pre-pulse inhibition of the startle reflex (PPI) has elucidated neural pathways that can inhibit the expression of the ASR. For instance, the substantial nigra pars retriculata (SNR), pedunculopontine tegmentum (PPT) and laterodorsal tegmental nuclei (LDT) have inhibitory influence upon the PnC, thus reducing the measured ASR [7-10]. These three mid-brain nuclei (inhibitory) receive projections from various forebrain areas, including the amygdala, BNST, and medial prefrontal cortex (mPFC). Thus, limbic system modulation of the ASR can occur through direct enervation of the PnC (excitatory) or indirect enervation through mid-brain nuclei.

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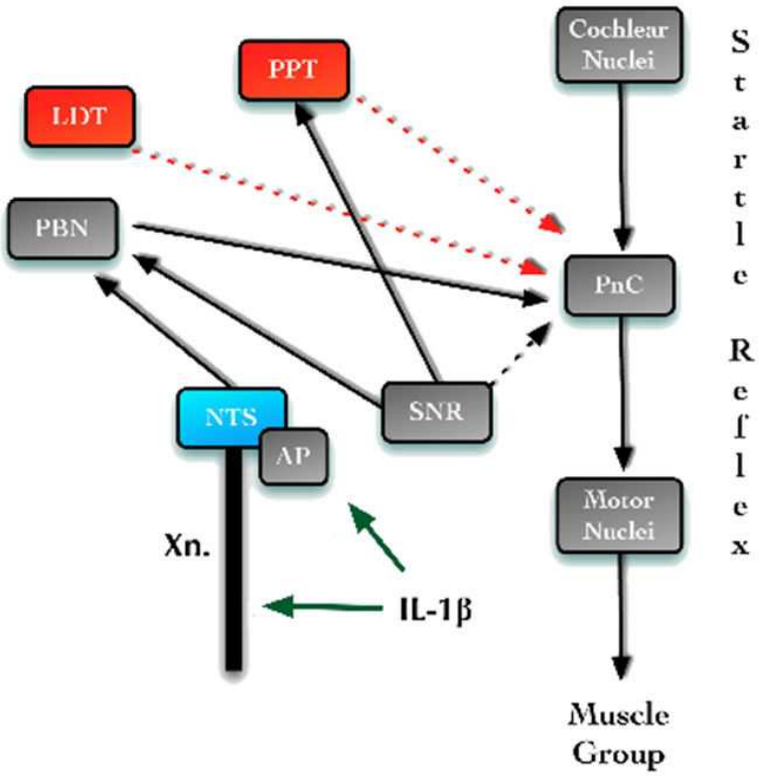

Figure 1. There are several nuclei within the midbrain/brainstem area that can directly modulate the intrinsic ASR circuit at the level of the nucleus reticularis pontis caudalis (PnC). Dashed red lines represent cholinergic inhibitory influences from the laterodorsal tegmental nuclei (LDT) and pedunculopontine tegmentum (PPT). Dashed black lines represent inhibitory GABAergic projections from the substantial nigra pars reticulata (SNR). A solid line from the parabrachial nucleus (PBN) is an example of a direct excitatory input to the PnC.

2.2. Abnormalities in the expression of the startle reflex in mental disorders

Over all other mental disorders, PTSD is associated with changes in the startle reflex. Commonly associated with exaggerated startle responses [11-14], higher or exaggerated startle reflex responses are a criteria symptom for the diagnosis of PTSD [15]. However, recent evidence suggests that this may not always be the case. In fact, others have reviewed the literature and found there are a significant number of reports where the startle responses in PTSD patients are not exaggerated [16]. More extreme, there are reports, albeit limited, where patients diagnosed with PTSD appeared to have blunted motor reflex responses to an acoustic stimulus [17, 18]. These populations had distinctive qualities that were different than those studies that had found enhanced startle reactivity in their PTSD patients. First, the one study was exclusively female [18] and the other had a majority of female subjects [17], suggesting there may be a sex difference in the presentation of ASR in females as a result of experiencing trauma. However, others have reported enhanced startle responses in a different population of women diagnosed with PTSD following automobile accidents [19]. Thus, a second distinction between the two studies that observed suppressed startle reactions, which should be considered, is that the trauma was specifically associated with being the target of violence [17, 18]. Although women with a PTSD diagnosis stemming from a prior rape have

not always exhibited blunted startle responses [20], this discrepancy may be due to individual differences and/or methodological differences in being sensitive to such changes, as some have reported laterality effects in PTSD patients, notably of those having been raped in the past [21]. A third quality of at least one of these two reports is that the subjects also exhibited symptoms associated with major depressive disorder [18]. This suggests stressful experiences may not cause a uniform change in sensory reactivity, and the expression of the coping response to the trauma may have psychophysiological ramifications that are quite different, both in terms of effects upon sensory-motor responding to acoustic stimuli as well as the full expression of symptoms.

There is evidence that symptoms associated with depression may also include a blunted reaction to acoustic stimuli. Patients designated as "depressed", having either a diagnosis of MDD or a significantly higher score on the Beck Depression Inventory (with or without additional neurological conditions), have been reported to exhibit blunted reactivity to acoustic stimuli, either with or without manipulations of affect [22-26]. Similarly, there is also evidence that bipolar disorder (BPD), the occurrence of at least one manic or mixed manic episode over the course of a patient's lifetime, is characterized by blunted startle reactions as well, even during periods of remission [27]. A study by Carroll and colleagues found patients suffering from BPD exhibit attenuated baseline startle, most notably in those having experienced mixed episodes, not pure mania [28]. These data suggest there is a neurobiology of startle suppression that may provide critical insight to the underlying biological conditions that cause areas of the brain to improperly process information, in this case sensory-motor responses.

2.3. Animal models utilizing stress to dampen startle reactivity

Across the studies that have documented reductions in the expression of the startle reflex in rodents, the common-most feature is that the magnitude of the response is dampened following exposure to a stressor manipulation. Reduced startle amplitudes have been documented in rats following: repeated 20 min restraint [29]; inescapable tailshock [30-32]; predator exposure coupled with an intraperitoneal injection [33]; immune-challenge [34, 35], and a single session of footshocks [36]. Interestingly, despite some differences in methodology, inescapable tailshock [30], inescapable footshock [36], and predator exposure with injection [33], all showed reduction in ASR measurements that could *not* be attributable to enhanced habituation to the acoustic stimuli. Yet, studies utilizing inescapable tailshock (in females) *have* established that exposure to the stressor condition causes a change in startle responsivity (the magnitude of the measured startle responses), not startle sensitivity (the threshold to elicit a certain percentage of startle responses). Thresholds for eliciting ASRs are not increased in the shocked females; instead, the magnitudes of the elicited startle responses are lower [31, 32]. This suggests, at least for the female stress model, that the presumed increased inhibition upon the activity in the intrinsic ASR circuit is occurring through the motor response aspect of the reflex arc. The muscles are simply not as mobilized when this condition is induced. This model condition has been termed by some *stress-induced startle suppression* [32, 34].

There are significant differences in the temporal characteristics of these different startle-suppression models in rodents. Inescapable tailshock causes a reduction in startle magnitude in female rats that is evident hours within exposure [31, 32], possibly lasting up to a day later, when the bouts of shock are expanded to a few consecutive days [30]. The footshock-in-

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duced suppression of startle reactivity is evident 4 h following stressor exposure [36]. The immune-challenge models parallel these stressor manipulations by causing reductions in startle reactivity within a couple hours of administration of the challenge [34, 35]. Thus, one interpretation of these data is that painful stressors are causing changes in the peripheral immune system, which, in turn, dampen startle reactivity during the time of their activity [34], on the range of hours. Following this logic, when females were tracked 4 and 8 days following tailshock, reductions in startle reactivity in the stressor-exposed rats did not reach statistical significance [30]. In contrast, the predator-exposure + injection model shows immediate suppression following the stressor exposure, which continues to be present 1 week later [33]. In addition, it is evident both under dark and light conditions [33], suggesting the change in the startle response is not occurring due to a change in reactivity to other stimuli that are known to modulate startle reactivity, such as light-enhanced startle [37]. Thus, this observance suggests that changes in ASR magnitude may be extended beyond the acute effects of stressor exposure that could be attributed to the short-term effects of immune signaling that would be in response to the injection (or possibly even shock).

3. Peripheral mechanisms of reduced startle reactivity

3.1. Hypothalamic-Pituitary Adrenal (HPA)–axis

Two interrelated mechanisms have been proposed as potential causes of startle suppression, the first being glucocorticoid hormone reception. Adamec and colleagues showed the reduction of startle magnitudes following combined cat exposure and saline injection could be blocked by substituting the saline injection with the glucocorticoid receptor antagonists RU-486 [33]. We subsequently tried to induce the effect in our female rats by administering the synthetic glucocorticoid agonist, dexamethasone. Startle responses were assessed 2 and 4 h following dexamethasone administration. As shown in Figure 2, the dexamethasone did not appreciably change the magnitude of the elicited ASRs, nor did it affect the number of ASRs elicited (data not shown). These findings suggest that the reception of corticosterone at the glucorticoid receptor is not sufficient to reduce ASR magnitudes. One possibility is that RU-486 blocked the suppressed startle, in that model system, via a non-glucocorticoid mechanism, for example via progesterone receptor antagonism. A connection to progesterone will be discussed further below as it pertains to a pro-inflammatory response mechanism, in contrast to an anti-inflammatory glucocorticoid response, but this finding is supported by previous work that shows elevations in circulating corticosterone are not necessary for corticotrophin releasing hormone to increase ASR magnitudes, despite stimulating increased activity in the HPA-axis [38]. Likewise, the suppression of ASR magnitudes in Occidental low saccharine consuming rats is not recapitulated by substituting corticosterone administration for the shock exposure [36]. Therefore, a role of glucocorticoids in the suppression of ASR magnitudes may be limited.

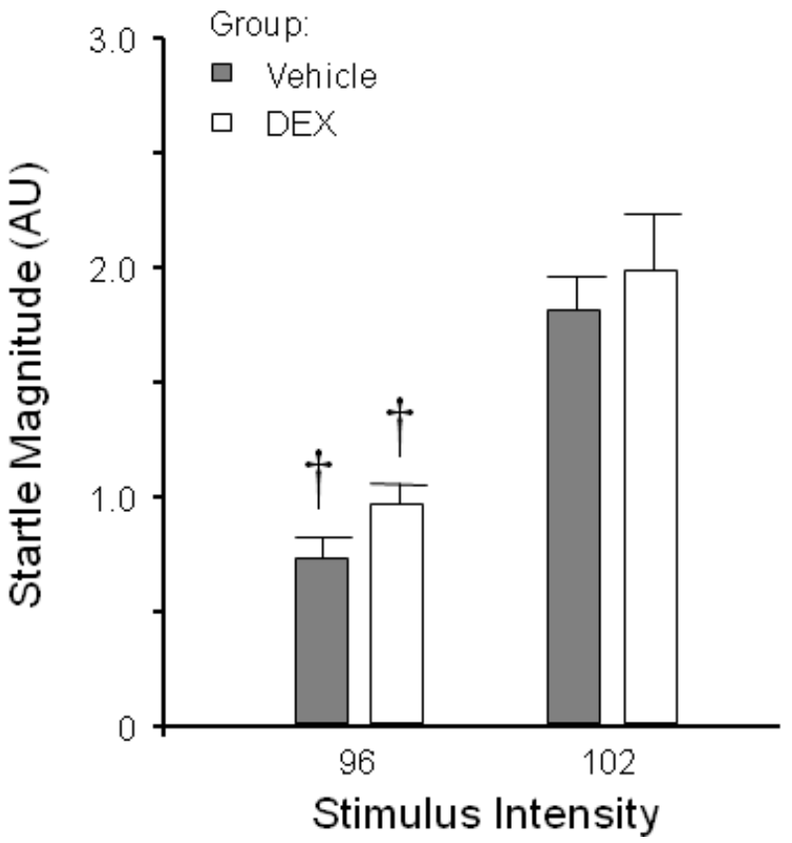

Figure 2. In order to increase binding at the glucocorticoid receptors, the synthetic glucocorticoid analog, dexamethasone, was administered s.c. (0.1 mg/kg) to female Sprague Dawley rats (n= 8-9). The magnitudes of the elicited ASRs only differed across the Stimulus Intensity, $F(1, 15) = 135.3$, $p < .001$, not drug administration. Data are collapsed over the 2 startle test sessions. A cross (†) represents within-group difference from the highest stimulus intensity ($p < .05$, Fishers LSD).

3.2. Pro-inflammatory cytokines

The second mechanism, which is intertwined with the HPA-axis, is the peripheral pro-inflammatory immune response. We first showed that a ovarian hormone-dependent suppression of startle magnitudes could be induced by a single injection of the pro-inflammatory cytokine interleukin (IL)-1β [34], an effect that appears to parallel that observed following tailshock [31]. This effect was later replicated in male rats using lipopolysaccharide (LPS) [35]. Still, peripherally released IL-1β elicits the release of glucocorticoids from the adrenal through stimulation of the vagus nerve, paraventricular nucleus of the hypothalamus, and pituitary gland, which provides an anti-inflammatory response to the pro-inflammatory signal [39-44]. In order to further delineate that pro-inflammatory cytokines, and not anti-inflammatory glucocorticoids, are necessary for stress-induced startle suppression, we compared the effect of inescapable tailshock upon the induction of ASRs in two strains of rats, specifically chosen because of their pro-inflammatory and glucocorticoid responsiveness to stressors. Low-glucocorticoid/high-pro-inflammatory releasing Lewis (LEW) rats [45-49] and high-glucocorticoid releasing Wistar-Kyoto (WKY) rats [50-52] were compared.

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Females of each of these strains were exposed to inescapable tailshock and subsequently tested for startle reactivity 1 and 3 h later. If pro-inflammatory signaling, not anti-inflammatory glucocorticoid release is critical for eliciting startle suppression, then LEW rats would exhibit suppression of the ASR, and the WKY rats would not. As shown in Figure 3, this is the case. This suggest the suppression of startle responsivity in female rats is more likely due to an overactive pro-inflammatory cytokine signaling response, instead of an overactive anti-inflammatory glucocorticoid response via the HPA-axis.

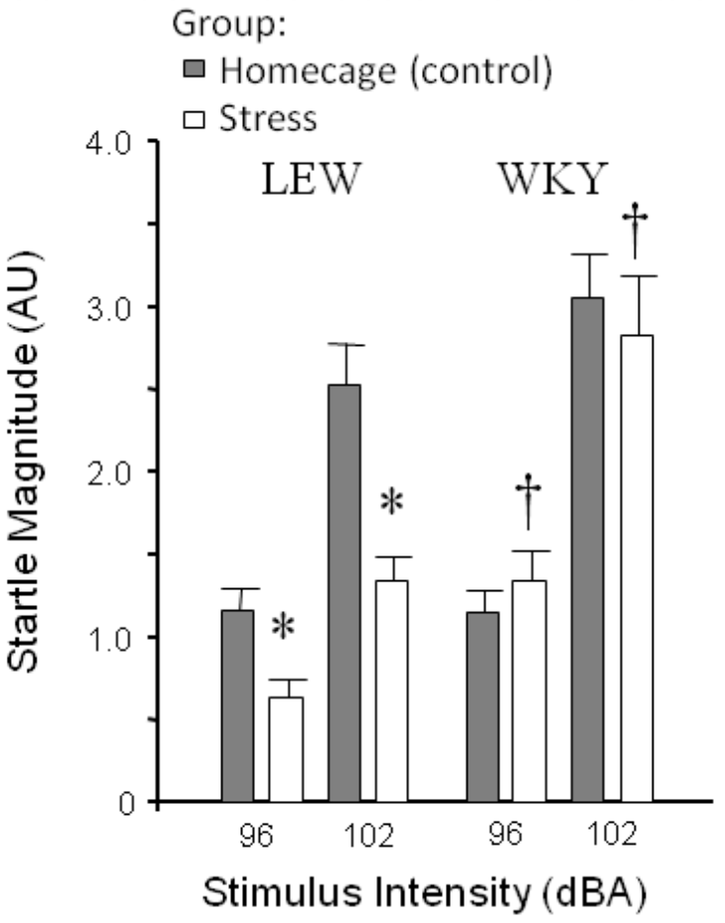

Figure 3. LEW rats exposed to the stressor differed from both their same-strain controls and the WKY groups on the measure of startle magnitude (responsivity). These impressions were confirmed by both main effects of Stimulus Intensity, $F(1, 36) = 285.0$, $p < .0001$, Strain, $F(1, 36) = 6.4$, $p < .02$, and Stressor exposure, $F(1, 36) = 5.3$, $p < .03$, as well as a marginal Strain x Stressor interaction, $F(1, 36) = 3.3$, $p < .07$. In addition to the expected differences in ASR magnitude due to Stimulus Intensity, $F(2, 72) = 186.5$, $p < .0001$, there were differences in the number of elicited startles across the two strains at the lowest stimulus intensity, with WKY rats having responded with more startles (4.5) than did the LEW rats (3.8) to 92 dBA stimulus. This impression was confirmed by a significant Strain x Stimulus Intensity interaction, $F(2, 72) = 3.0$, $p < .05$ (data not shown).

The hypothesis that pro-inflammatory cytokines are a necessary component in the suppression of startle responses following stress was further evaluated in the immune-sensitive Lewis rat strain by determining if elevations of peripheral IL-1β is sufficient to suppress startle reactivity in female rats. Startle responsivity has been found to be suppressed in female SD rats

[34], but, we questioned whether immune-sensitive Lewis rats would show either greater effect sizes in the suppression of the startle magnitudes and/or reduced startle sensitivity as well. As shown in Figure 4, both startle responsivity and sensitivity were reduced in female Lewis rats administered IL-1β. This confirms that pro-inflammatory signaling can influence both aspects of startle behavior, with sensitivity effects requiring a greater sensitivity to the pro-inflammatory signals or, possibly, greater elevations of the signal.

3.3. Prior immune challenge effects on stress-induced startle in SD rats

One consequence of the peripheral immune system having an effect on behavior, in this case sensory reactivity to acoustic stimuli, is that prior immune challenges may influence how future pro-inflammatory signaling or anti-inflammatory glucocorticoid responses influences behavior following stressor exposure. LPS is a commonly used endotoxin that elicits sickness behaviors due to a release of peripheral and central pro-inflammatory cytokines, followed by an increase in circulating glucocorticoids [53, 54]. Others have shown that immune challenges days prior to shock exposure causes a greater increase in glucocorticoid release in response to shocks [55, 56]; therefore, we used this known method of causing a sensitized glucocorticoid response to determine if a greater glucocorticoid release enhances or reduces the degree by which tailshock suppresses startle responsivity.

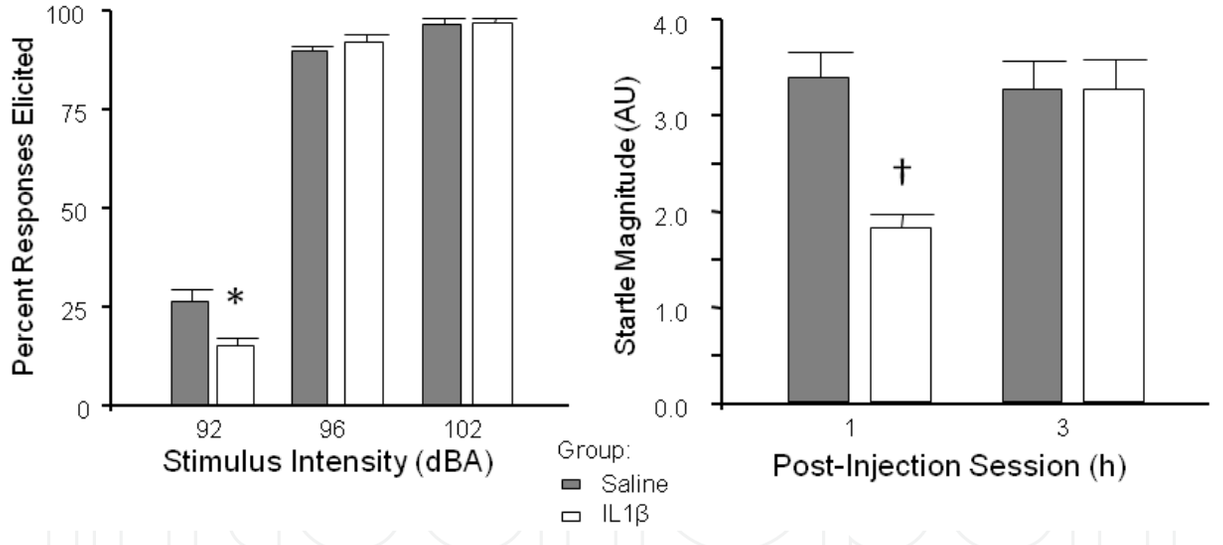

Figure 4. Female LEW rats (n = 16) exhibited significant differences in both startle sensitivity and startle responsivity measures following a single systemic injection of IL-1β (3 μg/kg, i.p.). Startle sensitivity was equally effected 1 and 3 h following administration and is shown collapsed over Session Time. Startle responsivity was only effected 1 h following administration; therefore, the 3 h time-point is not shown. An asterisk (*) represents a significant difference from saline-treated controls at the same stimulus intensity. A cross (†) represents a significant difference from saline-treated controls during the same test session (all $p < .05$, Fishers LSD).

We hypothesized that pro-inflammatory signaling causes stress-induced startle suppression; therefore, experiencing an immune challenge 3 days prior to shock would cause a sensitized anti-inflammatory release of glucocorticoids in response to inescapable shock, blocking the reduction of startle responsivity caused by the acute release of pro-inflammatory cytokines.

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As expected, the number of startle responses elicited did not differ based on prior treatment but did differ across stimulus intensity (data not shown); however, prior exposure to LPS reduced the effectiveness of inescapable shock to attenuate startle magnitudes (see Figure 5). Although LPS has a short-term suppressing effect upon the startle response [35], it both causes an acute increase in pro-inflammatory cytokines (and sickness behaviors) followed by an increase in anti-inflammatory glucocorticoid signaling. This "priming" effect upon the anti-inflammatory glucocorticoid response to shock is a likely mechanism for "buffering" the behavior from being affected. Again, this suggests the glucocorticoid response may actually counteract the suppressive effects originating from peripheral pro-inflammatory cytokine signaling.

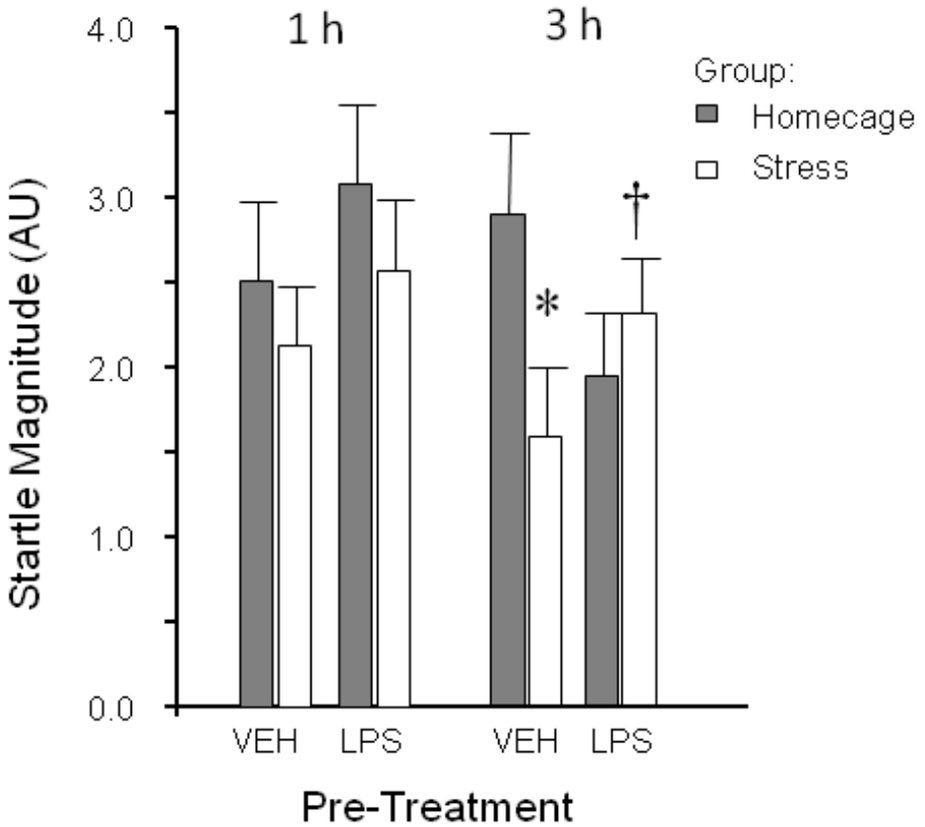

Figure 5. The expression of stress-induced startle suppression became evident 3 h following stressor exposure; however, this effect was blocked in those rats previously exposed to 30 µg/kg LPS (i.p.) 3 days earlier. These impressions were confirmed by a significant LPS x Stress x Session interaction, $F(1, 28) = 10.2$, $p < .005$. Hence, the pretreatment with LPS, which should have increased the glucocorticoid response to the inescapable tailshocks, blocked the suppression of startle responsivity following shock exposure. This suggests that prior experiences likely cause a more robust anti-inflammatory glucocorticoid response that actually *reduces* the influence of the peripheral immune pro-inflammatory immune response upon the areas of the brain capable of suppressing startle responsivity.

4. Central mechanisms of reduced startle reactivity

4.1. Neuroanatomy and endocrine modulation of startle suppression

As mentioned above, studies of pre-pulse inhibition of the ASR have elucidated neural circuitry that underlie the suppression of ASRs when they are immediately preceded by a salient auditory stimulus, for a review see [57]. Both the BNST and AMG have indirect projections to the PnC through the PPT [58]. Inputs from the PPT, LDT, and SNR to the PnC cause inhibition of the startle response [7, 9, 59, 60]. More specifically, it appears the magnocellular portion of the PnC has muscarinic receptors to receive the inhibitory cholinergic signal from PPT and LDT [61] and $GABA_B$ receptors receive the inhibitory signal from the SNR [62]. The question is whether these areas could provide more tonic inhibition of the ASR, outside of the attentional processes associated with PPI. For instance, it is known that lesions to the medial septum and the fimbra-fornix increase startle reactivity because these areas provide tonic inhibition upon the amygdala [63]; thus, removal of inhibition upon the amygdala increases tonic excitatory activity to the PnC (from the amygdala). In contrast, lesions to the noradrenergic cell bodies of the LC reduce startle response magnitudes, as these neurons probably serve a tonic excitation function upon the PnC [64]. Thus, there are circuits within the brain that are situated such that they could provide more tonic changes in the ASR.

Specific to the female startle-suppression model, a central mechanism that caused this change in reactivity should be influenced by the presence/absence of ovarian hormones [31, 32]. Ovarian hormones can have a significant impact on many of the neural structures associated with startle regulation. The cochlear nuclei [65], the nucleus accumbens [66], the hippocampus, [67] and the SNR [57] all exhibit changes in morphology, neurotransmission, and/or receptor expression with the presence of ovarian hormones. Yet, despite all these areas of influence, rodent studies usually do not find any differences in baseline startle reactivity across the estrus cycle or with hormone replacement [68, 69]; however, see [70] for an example of oral-contraceptive usage effecting baseline startle in women. When significant arousal or stress occurs in the rodents, however, the modulatory actions of ovarian hormones on startle become evident. For example, Toufexis and colleagues have shown the magnitude of CRH-enhanced startle is attenuated when progesterone levels are increased [71]. CRH is thought to enhance startle reactivity in the BNST via CRF1-type receptors [72-75]. The result is an increase in excitatory afferents signaling to the PnC [76]. One possibility is that progesterone, or its metabolite allopregnanolone, may decrease the excitatory signaling from the BNST to the PnC by increasing GABA inhibition in this structure [77]. However, in vitro, BNST CRF-1 receptors increase local GABA activity [78]. Thus, it appears that progesterone or allopregnanolone should facilitate the actions of CRH on startle, unless they act through different mechanisms within the BNST or outside of the BNST. On the other hand, progesterone also affects how IL-1β influences sexual receptivity [79], and both glucocorticoid receptor activation [77] and progesterone-induced changes in central neuroadrenergic activity [80] have been suggested to attenuate startle reactivity selectively in female rats. As shown in Figure 6, the administration of progesterone to ovariectomized

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rats appears to be necessary for IL-1β to suppress startle magnitudes. Thus, ovarian hormones are not sufficient to cause changes in startle reactivity in female rats. In fact, IL-1β appears to increase startle responsivity following estradiol pretreatment (17β-estradiol), whereas progesterone pretreatment sets the stage for IL-1β to suppress startle responsivity. Therefore, stress-induced startle suppression in female rats appears to necessitate a combination of the two factors, a peripheral pro-inflammatory immune response and the presence of progesterone.

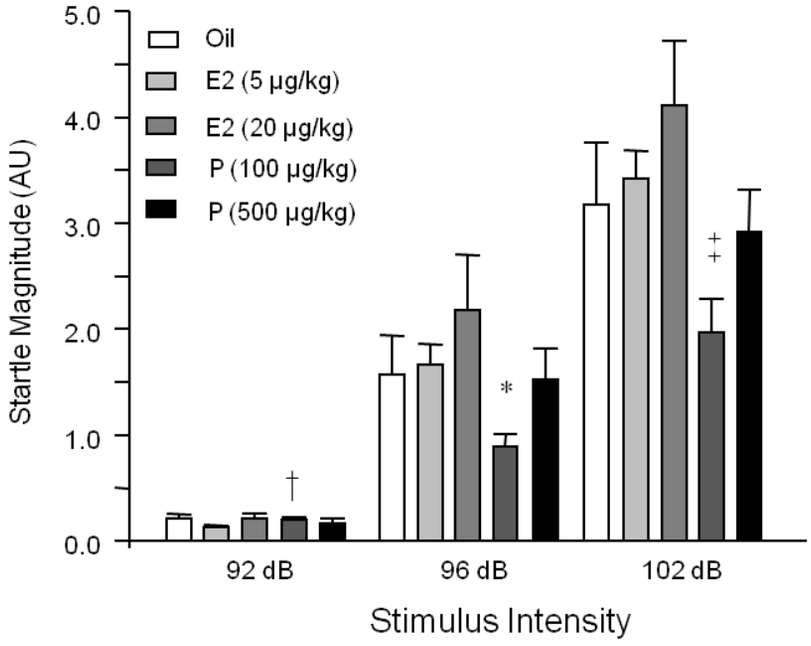

Figure 6. Startle sensitivity and responsiveness were assessed 2 h following IL-1β administration. Hormone treatment occurred 2 h prior to IL-1β injection. Differences in startles elicited (sensitivity) and the magnitudes of those elicited startle responses (responsivity) each were assessed via a 5 (Condition) x 3 (Stimulus Intensity) repeated measures ANOVA. No significant differences in startle sensitivity were detected (data not shown). However, a significant main effect of Stimulus Intensity, $F(2, 70) = 392.2$, $p < .001$ and a significant Condition x Stimulus Intensity interaction, $F[8, 70] = 2.1$, $p < .05$ were detected in the measure of startle responsivity (magnitude). An asterisk (*) represents a significant difference from all other groups. A single cross (†) represents a significant difference from the low estradiol dose group. A double cross (‡) represents a significant difference from both estradiol-treatment groups. All post-hoc tests used Fishers LSD ($p < .05$).

4.2. Evidence for limbic regulation of startle suppression

Peripheral IL-1β is known to have a significant impact on brain activity. Systemic IL-1 administration activates key afferent pathways in brainstem (lateral parabrachial nucleus and dorsomedial and ventrolateral medulla) and limbic system nuclei (BNST and central nucleus of the amygdala) [81]. In fact, peripheral IL-1β activates the amygdala and BNST more than i.c.v. administered IL-1β [82], probably because the vagal-mediated signals to these nuclei are more direct, to those nuclei via the NTS, than the diffusion of the IL-1β from the ventricles. Still, increasing peripheral IL-1β signaling increases NE and serotonin levels in these

brain areas [83] and noradrenergic metabolism in the paraventricular nucleus of the hypothalamus (PVN), locus coeruleus (LC), and amygdala [83]. In fact, as the IL-1β dose is increased, the amount of NE metabolism increases linearly in the amygdala, lasting as much as an hour [83]. It should be noted, this was not tested in the BNST. Yet, stimulation of α-adrenergic receptors also attenuate startle responses and facilitate non-associative habituation of the startle response [84-88]. IL-1β affects activity in the LC in a dose dependent manner as well, with low doses inhibiting activity and higher doses causing excitation; a process mediated by CRH at the time of IL-1β release [89]. Further, when the exposure to painful stimuli is prolonged or LPS is used to cause a significant pro-inflammatory response, additional release of central IL-1β occurs, especially in the hypothalamus [90, 91]. These data suggest that activity in the limbic system, monoamine activity in particular, is significantly affected by peripheral immune signaling.

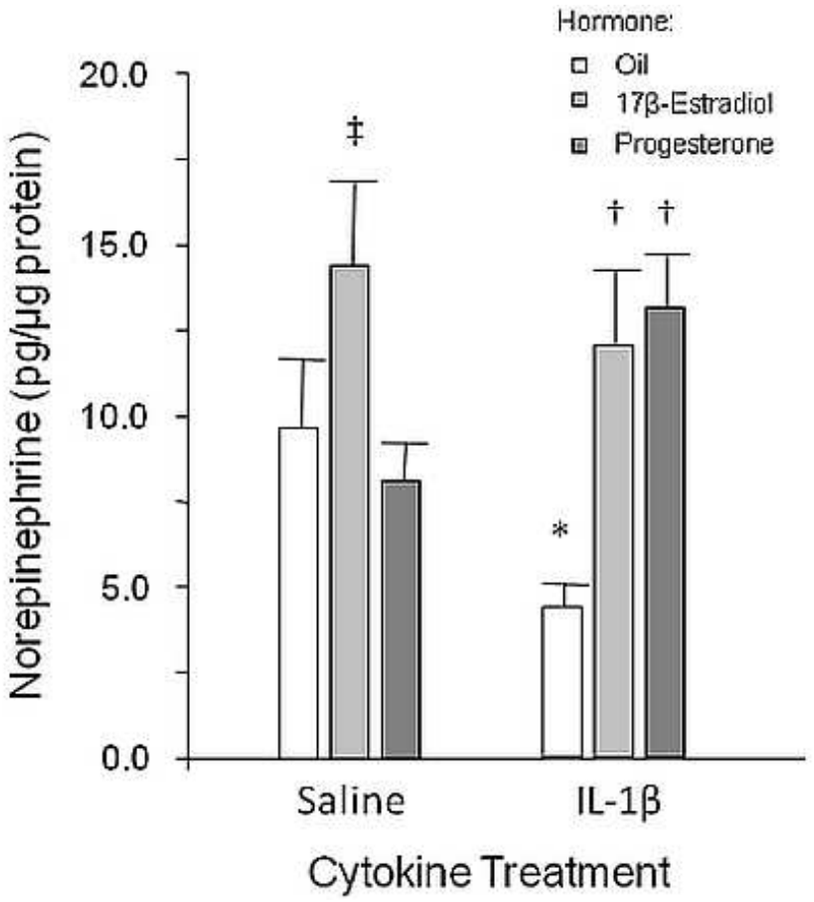

Figure 7. Significant effects of IL-1 treatment on NE levels in the BNST were observed in rats pretreated with progesterone (100 µg/kg, s.c.). This was confirmed by a significant Hormone x IL-1 interaction F (2, 42) = 4.5, p <.02. IL-1β treatment to oil-treated controls was associated with significantly lower NE levels than oil-treated saline-controls (*). IL-1β-administered rats, which were pretreated with either estradiol [20 µg/kg, s.c.) or progesterone, exhibited higher levels of NE compared to oil-pretreated rats that subsequently received IL-1β (†). In addition, the 2 hormone treated saline control conditions also differed from each other, with the estradiol-treated saline-controls exhibiting higher levels of NE than those pretreated with progesterone prior to saline administration (‡). All post-hoc tests utilized Fisher's LSD (p <.05).

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Based on the above logic, we hypothesized that the reduction in ASR magnitude occurring as a result of IL-1β administration to progesterone-pretreated female rats could be associated with changes in the central noradrenergic activity in one of the known modulatory nuclei of the acoustic startle response. Therefore, we measured norepinephrine levels in brain tissue-punches from 4 brain areas: BNST, amygdala, medial prefrontal cortex (mPFC), and dorsal hippocampus. As stated above, both the BNST and cAMG have direct excitatory projections to the PnC and indirect inhibitory connections via the PPT. The medial prefrontal cortex projects to the primary startle circuit via the LDT, whereas the dorsal hippocampus was included as an area that is both reactive to stress and ovarian hormone manipulation, but it is actually several synapses removed from the PPT. As shown in Figure 7, differences due to hormone pretreatment and subsequent IL-1β administration were found in the BNST, not in any of the other 3 areas.

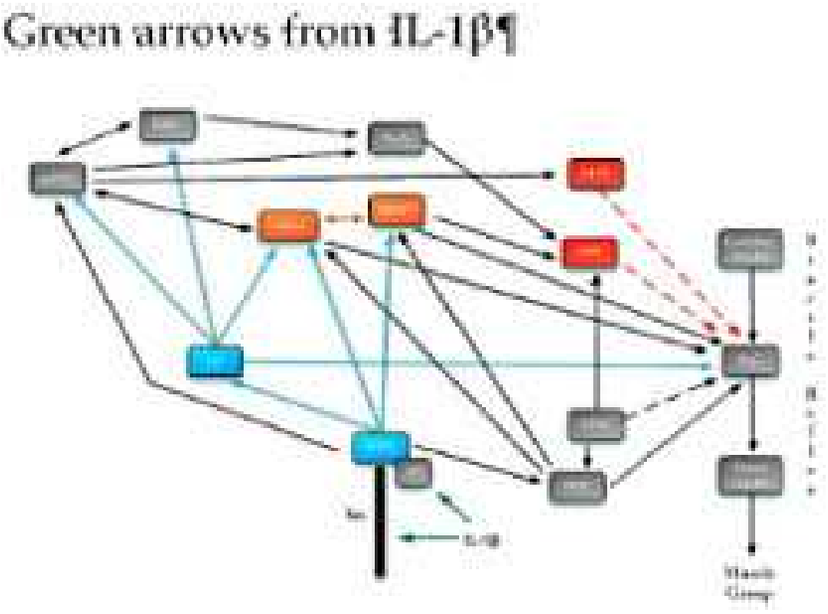

Figure 8. Beyond the direct connections of the brainstem/midbrain nuclei, there are many other nuclei that indirectly influence the modulation of the ASR. Graphically represented here are the noradrenergic projections (in blue) from the nucleus of the solitary tract (NTS) and locus coeruleus (LC) to the various nuclei of the limbic system that then modulate the ASR via the inhibitory brainstem/midbrain nuclei. Input to the NTS via either the from the vagus nerve (X n.) or diffusion of IL-1β across the blood-brain barrier in the nearby area postrema is necessary for the noradrenergic changes in the brain in response to peripheral pro-inflammatory cytokine signaling. As above, red lines denote cholinergic pathways, and dashed lines represent inhibitory circuits. The orange represents CRH-mediated neural circuits. See text for further details.

The role of the BNST in this cytokine-induced change in behavior is logical given recent work associating activity in this structure with changes in behavior associated with behavioral depression or sickness behavior. For example, an endotoxin-induced suppression of social interactions is both associated with increased activity in the BNST as well as reduced activity in the BNST when the suppressed behavior is blocked by IL-1ra [92]. Similarly, the behavioral depression exhibited in the forced-swim test can be reduced by stimulating the vagus nerve, leading to changes in brainstem nuclei activation (including the NTS) and also

activation of the BNST [93]. Others have shown NE release is elevated with stressor exposure in the BNST, which is necessary for some stress-induced behaviors [94, 95]. With particular attention to the startle reflex, the BNST is commonly associated with enhancing startle reactivity [2, 96]. However, as shown in Figure 8), there is an inhibitory pathway from the BNST to the PnC via the PPT that has been examined as a cholinergic mechanism for eliciting PPI [97, 98]. Further, PPI has been shown to fluctuate over the estrus cycle, while not being sensitive to apomorphine disruption, implicating a non-dopaminergic mechanism for these hormone-induced changes in female pre-pulse inhibition, which could rule-out a role of the substantia nigra in this process [68]. In addition, the changes in measured NE levels in the BNST are consistent with previous studies citing peripheral IL-1β administration as a trigger for central noradrenergic activity [82, 99].

There is evidence that could suggest a connection between the known effects of peripheral cytokine activity upon brain noradrenergic activity (most reported males) and an ovarian hormone influence upon these processes. For one, there is growing information pertaining to ovarian hormone influences on noradrenergic activity initiated from the NTS. Many of the brainstem noradrenergic nuclei, including the NTS, exhibit cyclic changes in estrogen and progesterone receptors [100]. Removal of ovarian hormones with or without hormone replacement particularly has a significant impact on NTS physiology. Specifically, the mRNA for prolactin-releasing peptide (PrRP) in noradrenergic neurons is decreased by ovariectomy and increased with subsequent replacement of either estradiol or progesterone [101]. Although the PrRP mRNA levels are reported to not change significantly across the estrus cycle in the NTS, an inspection of the data suggests the levels are a bit higher during proestrus [102]. PrRP labeling in the NTS is also preferentially sensitive to painful stressors, such as tailshock [103]. Estradiol has also been reported to increase neural inhibition in the NTS [104]. These data suggest ovarian hormone influences on NE NTS physiology could occur through changes in the regulation of a co-expressing neuropeptide. This could serve a filtering function for the vagal activity representing immune activity changes in the periphery, as the NTS projects its NE efferent connections to key areas involved in arousal and sensory reactivity, such as the BNST, AMG, hypothalamus, and parabrachial nucleus [105]. For example, core body temperature increases from peripheral IL-1β occur for a longer period of time during proestrus (compared to diestrus) apparently do to the actions of progesterone [106]. Although it is clear hypothalamic cyclooxygenase is the necessary mechanism for this effect [107] the noradrenergic input to the hypothalamus is required and may be changed as well [108]. Therefore, there are anatomical and pharmacological reasons to link NTS noradrenergic projections to the BNST as the primary pathway by which changes in vagal activity could influence startle responsivity through known inhibitory circuitry.

Other possible mechanism for startle suppression could occur as a cascade of effects that begin with the hormone-specific effects upon NE in the brain, but end with non-specific hormonal influences upon 5-HT. NE was shown above to be changed in the BNST following systemic increases in IL-1β, confirming the results of others showing noradrenergic activity increases within 30 minutes of a peripheral injection of IL-1β and may last 2 hours [109, 110]. Importantly, as proposed above, the effect of systemic IL-1β injections on brain NE in rodents is dependent upon transmission in the vagus nerve [111]. The effects of peripheral IL-1β on 5-HT are quite different in terms of timing, route, and influence of ovarian hormones. First the increases observed in brain serotonin metabolism are evident 2-4 h following IL-1β administration and,

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at least in male rats, are reported to be less region specific (compared to NE activity changes) [110]. In addition, the effects of peripheral IL-1β on brain 5-HT are not dependent upon the vagus nerve in male mice but neither are the effects upon brain NE activity [112]. Thus, it is not known if 5-HT requires the same pathway as IL-1β to effect central 5-HT activity, but the difference in the temporal cascade would suggest such a difference is logical. Further, as shown in Figure 9, the same peripheral IL-1β injections that elicited a hormone-dependent change in BNST NE levels caused an increase in 5-HT activity in both estradiol and progesterone-treated female rats. This somewhat conforms to the data previously describing less specificity in the upregulation of 5-HT activity, although we did not observe this pattern beyond the BNST.

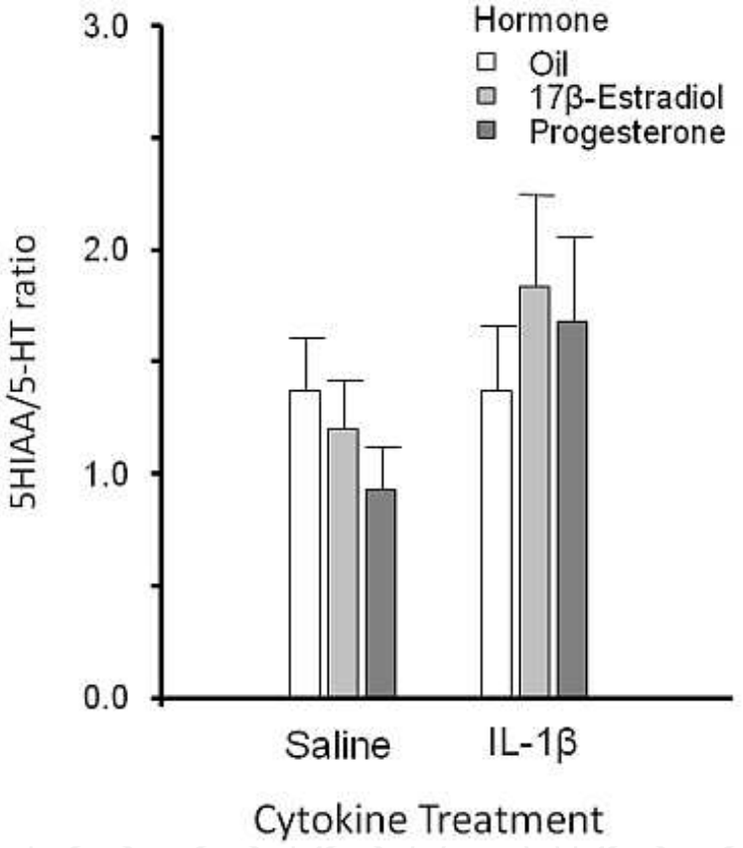

Figure 9. Serotonin activity (5HIAA/5HT ratio) appears to be increased in the BNST of hormone-pretreated OVX female rats 2 h after a systemic injection of IL-1β, as suggested by a marginal effect of IL-1β, $F(1, 42) = 3.6$, $p < .06$.

5. Immune mechanisms following the acute pro-inflammatory response: Recovery or maintenance?

5.1. Recovery of startle responsivity

The peripheral immune system also has counter-inflammation mechanisms that could also be potential mechanisms for what appears to be a pro-inflammatory cytokine-mediated ef-

fect. Thus, another response to pro-inflammatory cytokine release, is the increase in the endogenous IL-1 receptor antagonist (IL-1ra), which has been shown to attenuate the reductions in food-intake elicited by systemic administration of LPS or IL-1β [113]. Our hypothesis was that elevations in IL-1ra, from systemic administration, would counteract the effects of IL-1β. Thus, IL-1ra was administered systemically, followed by an assessment of startle reactivity 1 and 3 h later. As shown in Figure 10, the peripheral immune mechanism for stifling the pro-inflammatory response of IL-1β is sufficient to increase startle sensitivity. This suggests the nervous system is responsive to elevated acute pro-inflammatory signaling, suppressing startle, and elevations in the counter-active IL-1ra, increasing sensitivity to acoustic stimuli. These interactions illustrate the constant inter-relationship between the peripheral immune system and the nervous system regulation of sensory-motor activity.

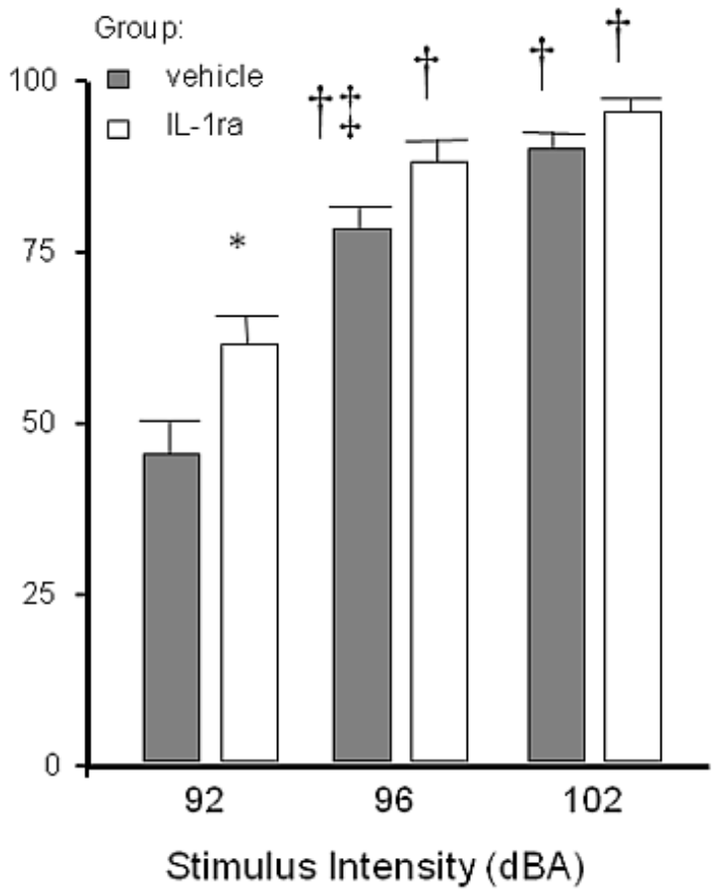

Figure 10. Startle magnitudes in female SD rats (n = 7) were not affected by the administration of IL-1ra (10μg/kg); however, ASRs were elicited more often following the administration of IL-1ra. These impressions were confirmed by a significant main effect of Drug F (1, 12) = 9.7, p <.01. The higher sensitivity to the stimuli was superimposed upon the general difference in elicited startles across the three intensities, as reflected by a main effect of Stimulus Intensity, F (2, 24) = 67.4, p <.0001. An asterisk (*) represents a significant between-group difference from the vehicle-treated controls at the same intensity. A cross (†) represents a significant within-subject difference from the lowest intensity, and a double cross (‡) represents a significant within-subject difference from the highest intensity (all p <.05, Fishers LSD).

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5.2. Immune influences on serotonin synthesis: A possible central mechanism of continued suppression?

Serotonin (5-HT) is an essential modulator of the startle reflex and disruption of serotonin synthesis and metabolism has been shown to result in startle suppression. As shown in Figure 11, during the synthesis of serotonin, L-tryptophan is converted to 5-hydroxytryptophan (5-HTP) by the enzyme tryptophan hydroxylase. In a subsequent reaction, 5-HTP is converted to 5-HT by the enzyme L-aromatic amino acid decarboxylase. Disruption to any part of the 5-HT synthesis pathway is capable of reducing whole brain levels of serotonin resulting in unique abnormalities to the startle reflex. For example, when normal fasted women were tested after having ingested a tryptophan-free amino-acid mixture, the result was lower ASR magnitudes compared to those that received a mixture with L-tryptophan in its contents [114]. When a similar study was conducted in men, a non-significant trend for the same effect appears evident, although it was represented in the analysis as a failure to obtain significant PPI [115]. Alternatively, increasing tryptophan catabolism has also shown to affect PPI. Increasing levels of kynurenine, the first product of tryptophan degradation via indoleamine2, 3-dioxygenase, disrupts PPI in male Sprague-Dawley Rats [116]. Thus, the balance of serotonin and kynurenine is a likely secondary mechanism the body uses to modulate startle sensitivity and responsivity to stimuli.

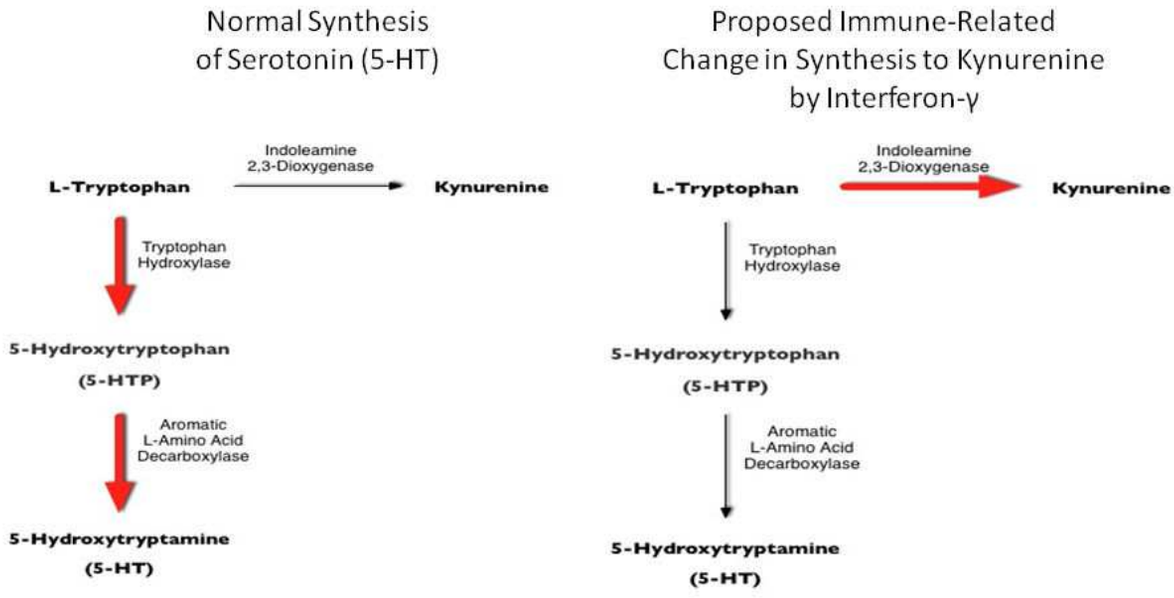

Figure 11. The normal synthesis of serotonin (5-HT) involves the metabolism of tryptophan to 5-hydroxytryophan by tryptophan hydroxylase; however, in the presence of interferon-γ, another, competing enzyme, indolamine1,3-dioxygenase is upregulated. The result of this shift in the metabolism of tryptophan towards the formation of kynurenine is a reduction in the amount available for metabolism towards the formation of serotonin (i.e. serotonin depletion).

In addition to exhibiting reduced startle responses [18] women exhibiting PTSD, linked to previous intimate partner violence, also exhibit greater circulating levels of interferon (INF)-

γ [117]. INF-γ is a downstream Th-1 mediated signal from the pro-inflammatory IL-1β signal and is a potent inhibitor of 5-HT synthesis, decreasing the amount of tryptophan available for 5-HT production. In the presence of IFN-γ, tryptophan is shunted to kynurenic acid synthesis by increasing activity of indoleamine2, 3-dioxygenase [118]. An intermediary signal between IL-1β and INF-γ is IL-2. Female rats treated with IL-1ra (to combat the induction of EAE) exhibit an attenuated IL-2 response [119], which would, presumably, decrease INF-γ signaling (see Figure 12). There is limited experimental evidence that has focused upon delineating INF-γ or IL-2 effects on startle reactivity in rats, and those that have been conducted use an early development administration paradigm to assess later changes on behavior (e.g. [120]). However, one study conducted in mice did access acute IL-2 effects upon startle reactivity and reported no change in behavior [121]. Unfortunately, that study did not test more than one time-point and only utilized male mice.

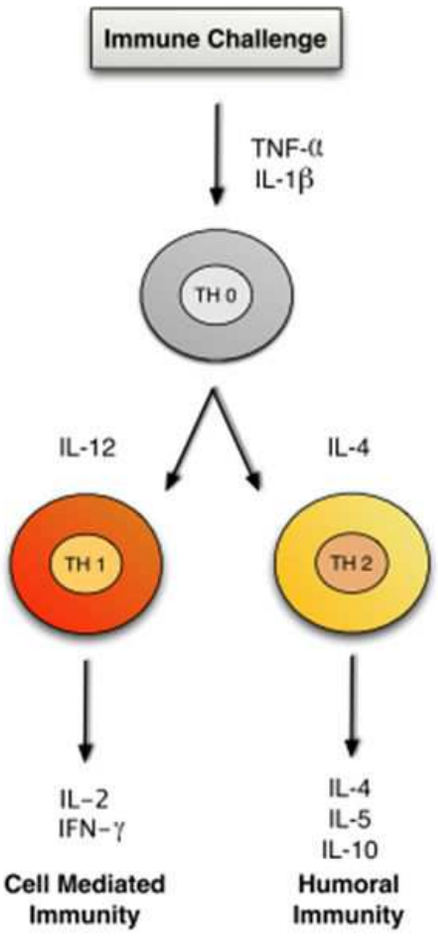

Figure 12. The initiation of an inflammatory response begins with the non-specific macrophage pro-inflammatory response (Th0), which then diverges into either a Th1 (cell-based) or Th2 (humoral-mediated) response. There is evidence that suggests ovarian hormones may influence the path of the subsequent immune cascade from the Th0 response. To date, the Th1 response has been more intently studied for its possible role in effecting behavior (i.e. causing changes in behavior).

Given the lack of data pertaining to IFN-γ effects upon startle sensitivity and responsivity, we conducted a study focusing on determining whether IFN-γ could change ASR sensitivity or responsivity. As stated above, LEW rats exhibit greater pro-inflammatory responses to infection than do other strains; therefore, we tested whether acute administration of IFN-γ is sufficient to reduce startle reactivity, presumably from reducing serotonin availability. Although still preliminary, our results suggest IFN-γ may have a bi-potential effect on startle sensitivity. The higher dose of IFN-γ caused an apparent decrease in the percentage of startles elicited 1.5 h following injection, whereas the lower dose caused significantly more startles to be elicited than the high dose (see Figure 13). This is an important distinction, for it suggests that reduced startle responding due to IFN-γ (and possibly low serotonin tone) is due to a decrease in the ability to sense a startling stimulus, rather than the ability to mount the physical response (although there are trends suggesting that responsivity may be decreased as well with higher doses). Hence, there may be more than a hypothetical link between stress, IL-1 release, and an identified difference in basal immune functioning in a population of women with PTSD that have also been described to have blunted startle responses. There may be instances where the downstream Th1-response is elevated, thus causing a seemingly similar "blunting" of the ASR but the suppression is different in form and occurs through different neural pathways.

6. Clinical applications

The suppression of startle reactions has only gained significant attention in the past decade, and, as researchers have looked for *changes* in startle responses (not just exaggerations), suppression has been observed in anxiety disorders (i.e. PTSD), MDD, and BPD. However, what does it mean when a specific, directional change in a reflex behavior is observed across these different diagnoses? The answer may lie in what is generally called *comorbidity*.

When one considers stress-related mental disorders, typically, anxiety disorders, MDD, BPD, and maybe even schizophrenia are cited as examples, but how distinct are anxiety disorders from MDD or MDD from BPD? In all cases, there is an overlap of various symptoms that could be experienced with any of these diagnoses. The DSM clinical criteria do provide some flexibility in categorizing subjects into the different classes of disorders. What that allows for are physiological conditions that are not specific to just one of these classes, and chronic or phasic abnormalities in the activities of the peripheral immune system could be common in some patients that meet the criteria for PTSD, the non-mania phase of BPD, or even MDD.

For example, there is a growing body of literature that suggests abnormal immune system signaling may be at the core of BPD. Several studies have shown abnormalities in the cytokine profiles of BPD patients, with differences present in both depressed and manic subpopulations [122-124]. Multiple studies have shown a characteristic increase in TNF-α among both bipolar depressed and manic patients [122, 123], whereas patients suffering from bipolar mania commonly exhibit decrease in IL-1β, IL-2, and IFN-γ. When stimulated with LPS,

a common procedure used to model behavioral depression in animals, the monocytes from non-lithium treated patients exhibit a decrease in the production of IL-1β and an increase in IL-6, compared to healthy controls. This abnormality was shown to be reversed in lithium treatment patients [125]. This suggests a by-product of lithium administration may be an influence on the pro-inflammatory response signals in the periphery. Additionally, Boufidou and colleges found that lithium is capable of down regulating the production of IL-2, IL-6, IL-10 and IFN-γ from peripheral blood lymphocytes in BPD patients, and a similar down regulation of pro-inflammatory cytokines was observed in previously non-medicated BDP after three months of lithium treatment [126]. These data further implicate a peripheral immune mechanism for BPD that is normalized by lithium treatment.

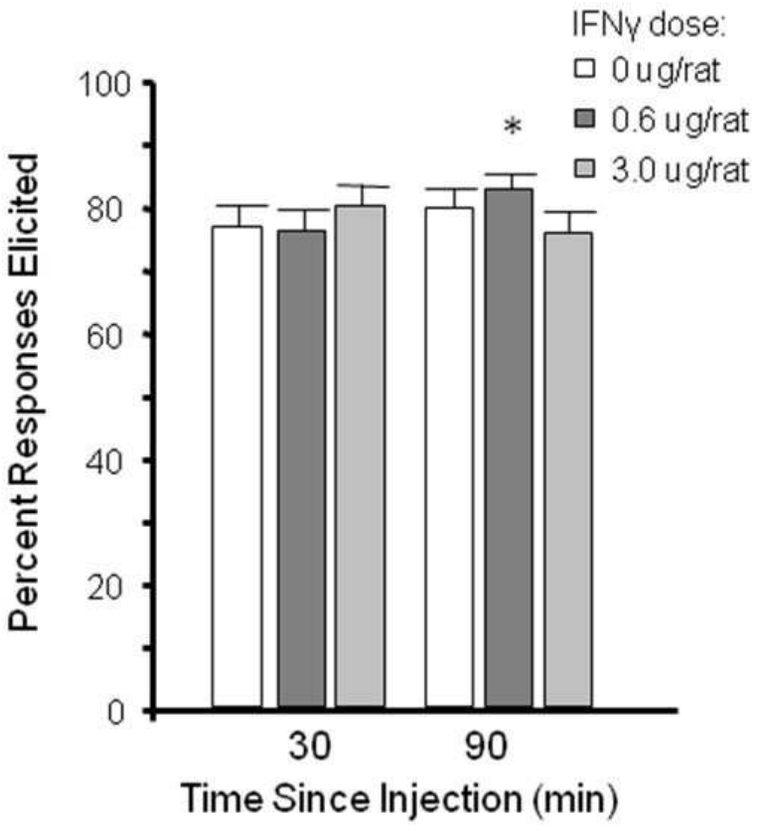

Figure 13. Startle sensitivity and responsivity were assessed 30 and 90 min following an acute systemic injection of IFN-γ (n = 16). Startle sensitivity was significantly altered by the specific dose administered. The low dose showed an increase in elicited startles over time, whereas the high dose showed a reduction in elicited startles over time, IFNγ x Session F (2, 29)= 3.3, p <.05. An asterisk represents a significant difference in the low-dose group at the 90 min test as compared to the same time high-dose and the 30-min low-dose test.

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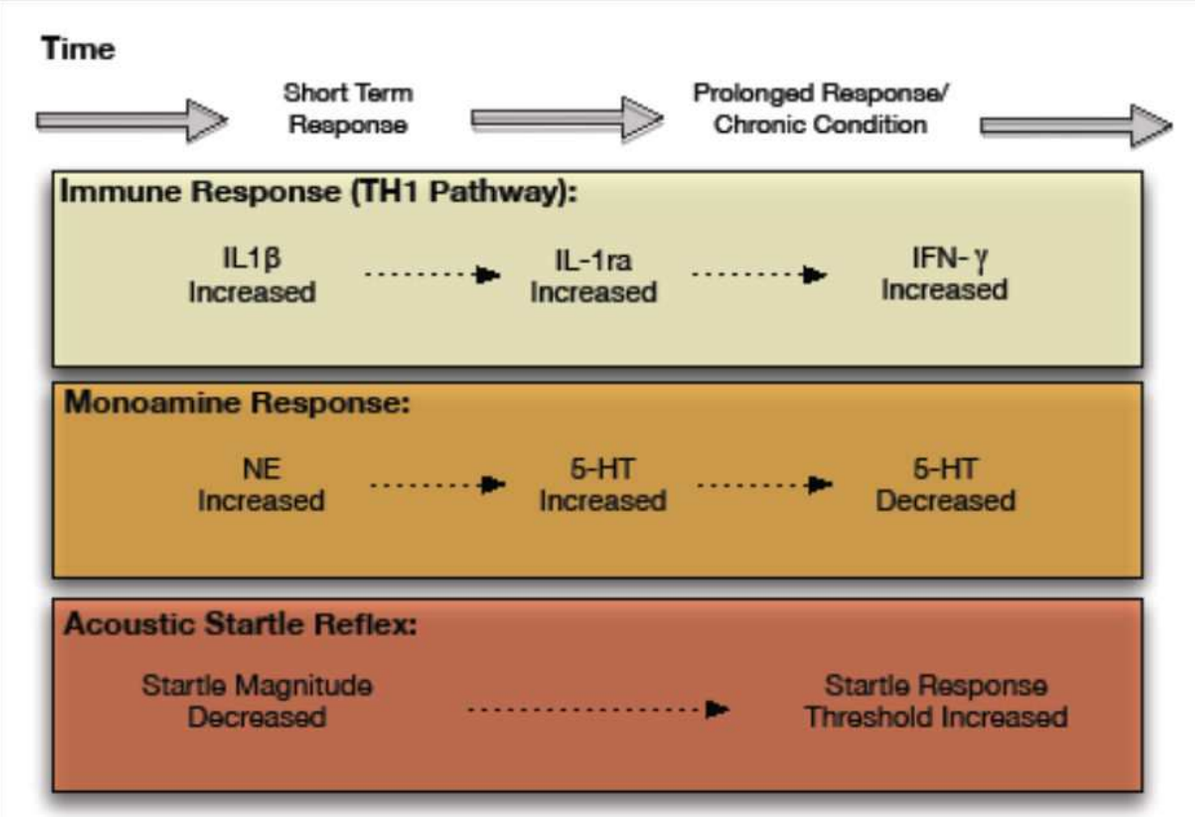

Figure 14. Based on the literature and the collected data from our laboratory, concerning the modulation of the ASR, we propose the following cascade of events may occur as a result of stressor exposure in our female rat model. First, the acute-phase (pro-inflammatory) response causes a transient reduction in startle responsivity (magnitude) that appears to last as long as IL-1 continues to be elevated above the levels of circulating IL-1ra. IL-1ra serves to normalize the response; thus, when the levels of IL-1ra are elevated to a sufficient degree, it causes an increase in ASR sensitivity (a rebound effect). However, in the cases where the stressor exposure is prolonged and/or severe enough to engage a downstream Th-1 response (i.e. increase IFN-γ signaling), then a reduction in ASR sensitivity occurs, whereby the sensory threshold for eliciting the response is increased. This could cause a chronic condition where ASRs are "blunted" in people with conditions ranging from PTSD to MDD to BPD.

The ASR could have a potential use as a functional index of abnormal peripheral immune functioning; thus, if the ASR is suppressed, it may represent an elevated level of pro-inflammatory or Th1 signaling in the patient. This could be of great importance from a therapeutic standpoint when one considers the suppressive effects of IL-1 upon sexual motivation in female rats are attenuated by indomethacin and ibuprofen [127]. Although blocking prostaglandin synthesis [128] or knocking-out the prostaglandin EP2 receptor does not change startle reactivity [129], prostaglandin EP1 knock-out mice do exhibit higher startle magnitudes compared to their wild-type control strain [130]. This suggests that EP1 receptors are in a position to serve as neuroimmune mechanisms to inhibit startle responsivity as well. Still, beyond the possible pharmacological implications, blunted reactivity to stimuli can have profound effects on other neural processes as well, and may explain some of the other symptoms associated with anxiety, MDD, or BPD. For instance, when the same dose of IL-1β, sufficient to blunt startle responsivity in female SD and Lewis rats, is administered to female SD rats prior to a simple associative learning procedure the rate of learning is

slowed. This effect is attributed to a reduction in the neural representation of the unconditional reflexive response (i.e. the response is weaker), causing less optimal neural representation of the behavioral response to the predictive, conditional stimulus [131]. The implication is that associative learning may be impaired by either acute or chronic elevations in pro-inflammatory or Th1 cytokines. Interestingly, this pattern of effect is not observed in male rats, at these low to moderate dosages of IL-1β; in fact, these learning processes are facilitated [132, 133]. Thus, the ASR can serve as a tool to better understand the blunting of sensory reactivity, but may also have implications for more complex associative learning processes as well. In Figure 14, we present our theory as to how the ASR may be changed over time as a function of neuroimmune interactions between peripheral cytokine signaling (specifically the acute pro-inflammatory response and the downstream Th-1 response) and brain monoamines.

7. Conclusions

The evidence accumulated from these experiments favors a pro-inflammatory mechanism, over a HPA-axis glucocorticoid mechanism, as the necessary pathway that ultimately leads to the suppression of startle reactivity following stressor exposure. This finding adds to the ever-growing evidence that peripheral immune signaling has a significant role in influencing how the nervous systems functions. In this particular case, we have illustrated how a simple behavioral reflex can be dampened by pro-inflammatory signals, in the absence of any physical injury. This shows abnormal levels of peripheral immune signaling could lead to perceived symptoms reported by patients with PTSD, MDD, or BPD.

Biological differences in how different animals respond to stressor may reflect vulnerability factors for experiencing different symptoms associated with stress-related disorders, such as PTSD, MDD, and BPD. Thus, differences observed in the literature concerning startle reactivity in female PTSD patients (e.g. [18, 19]) could be due to the types of stressor exposure or individual differences in biological responses. In addition, one cannot rule-out the role of coping mechanisms. In fact, one could hypothesize that the suppression of startle is an evolutionary selected response that keeps individuals within a species from continuing to fight a "losing battle". If this were the case, then it would be logical for the immune system to play a role in that trigger-mechanism and not the HPA-axis. The HPA-axis is designed to maintain the fight-or-flight response [134], which would be in opposition to a behavioral suppression coping response. Others have proposed females are particularly selected to engage in alternative coping strategies that are in opposition to the fight-or-flight response [135], and one possibility is that signal reception of the peripheral immune response by the central nervous system is an early point of diversion in stress coping strategies between males and females. This could provide inherent propensities to respond differently, but, at the same time, could be modified by experience. Such propensities could translate into vulnerability factors for abnormal behaviors where that response becomes, potentially, maladaptive.

It is well documented that more women experience anxiety disorders and affective disorders, and there is a significant degree of comorbidity across these disorders – especially as cases become more severe [136]. There are many potential reasons for the higher rates re-

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ported in women. For instance, some have recently suggested there is a link between ovarian hormones and the occurrence of specific peptide isoforms that modulate stress responsiveness and fear conditioning [137]. The data presented here provide another example of how ovarian hormones can influence physiological processes associated with stress responsiveness. The role of progesterone in this immune model of startle suppression is particularly intriguing since progesterone can amplify the pro-inflammatory response through macrophage migration inhibitory factor [138]. This endocrine influence could, potentially, cause more Th1 signaling to occur, which, we hypothesize leads to an increase in IL-1β, causing more Th1 signaling to occur, eventually leading to an increase in IFN-γ release and subsequent reductions in sensitivity to auditory stimuli. If that same individual has central nervous system vulnerabilities, such as a particular peptide isoform, then, in addition to an apparent blunted startle response, the patient may also be exhibiting flashbacks due to enhanced neural processing of fear-associated memory. Thus, female vulnerability for anxiety and depression symptoms can be seen as a product of multiple mechanisms that modulate the female physiology and behavior in a manner that, at times, may even be counter to fight-or-flight, but, nonetheless lead to changes in nervous system functioning, causing the expression of a particular set of behavioral symptoms.

There is a growing literature pointing towards a complex interaction between the central nervous system and the peripheral immune system that underlies anxiety or affective disorder vulnerability and/or the presence of acute symptoms [139-143]. The utility of being able to use species-common measures, such as the startle response, has been advantageous to researchers in aiding them to understand how the brain functions under normal and abnormal conditions. Here we illustrate how such measures can be applied to the understanding of psychoneuroimmune interaction as they pertain to the influence of the peripheral immune system upon the brain and behavior. As we gain a greater understanding of the signaling cascades in the peripheral immune system, delineating how those signals affect the brain will continue to be important for our future understanding of the etiology of mental illnesses.

Acknowledgements

This research was supported by a U.S. Department of Veterans Affairs Merit Review research program to KDB and program support through the UMDNJ – Stress & Motivated Behavior Institute. The described experimentation was conducted with approval by the VANJHCS Institutional Animal Care and Use and Research and Development Committees, in accordance with the NIH Guide for the Care and Use of Animals. The authors want to thank Toni Marie Dispenziere, Tracey Longo, Ian Smith, and Paul William Ong for their technical assistance in conducting the experiments. Some of the described work was included in the undergraduate honors thesis of Mr. Ong. The authors also thank Dr. Victoria Luine for the use of the laboratory in the processing and measurement of the brain monoamine data.

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