

Review article

Cytokines, stressors, and clinical depression: Augmented adaptation responses underlie depression pathogenesis

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Abstract

By influencing the central nervous system, cytokines, which regulate immune function innately and adaptively, may play a key role in mediating depression-like neuro-behavioral changes. However, the similarity between cytokine and stressor-effects in animal models raises a question about the degree to which behavioral and neurochemical outcomes of cytokine challenge represent depressive disorder per se. The present review attempts to illustrate the degree of overlap between cytokines and stressors with respect to their effects on neurochemistry and behavior in animal models. The review also shows how short-term effects of cytokine exposure in typical animals may be discerned from characteristics that might otherwise be described as depression-like. By comparing outcomes of immune challenge in typical rodent strains (e.g., Sprague–Dawley [SD], Wistar) and an accepted animal model of depression (e.g., Fawn Hooded [FH] rodent strain), differences between short-term effects of cytokines and depression-like characteristics in rodents are demonstrated. Additionally, because it is known that preexisting vulnerability to depression may affect outcomes of immune challenge, we further compare immunological, biochemical and behavioral effects of cytokines between SD and FH rodent strains. Interestingly, the acute neurochemical and behavioral effects of the cytokine interleukin 1 α (IL-1 α) reveal stressor-like responses during behavioral habituation in both strains, though this appears to a stronger degree in FH animals. Further, the subacute response to IL-1 α vastly differed between strains, indicating differences in adaptive mechanisms. Thus, stressor-like effects of immune challenge, particularly in FH animals, provide validation for recent “cross-sensitization” models of depression pathogenesis that incorporate immune factors.

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Abbreviations: FH, Fawn Hooded; HPC, hippocampus; HPA, hypothalamus-pituitary-adrenal axis; 5-HIAA, 5-hydroxyindoleacetic acid; IL-1 α , interleukin-1 alpha; IL-1 β , interleukin-1 beta; IL-1ra, interleukin-1 receptor antagonist; IL-2, interleukin-2; IL-6, interleukin-6; IL-10, interleukin-10; LPS, lipopolysaccharide; LC, locus coeruleus; NE-ergic, noradrenergic; NE, norepinephrine; NMI, neuromolecular imaging; PFC, prefrontal cortex; 5-HT, serotonin; 5-HT-ergic, serotonergic; SD, Sprague–Dawley; TNF α , tumor necrosis factor alpha.

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1. Introduction

Mounting evidence that immune activity influences central nervous function supports the position that cytokines (e.g., IL-1, IL-2, IL-6, TNF α , etc.), perhaps as much as neurotransmitters, play a role in regulating cognition, affect, and behavior. In addition, central output can impact immune function (Fig. 1). In experimental animals, the behavioral (e.g., “sickness behavior”, Maier and Watkins, 1998; Koonsman et al., 2002) and physiological (e.g., hypothalamic-pituitary axis [HPA] activation, Besedovsky et al., 1986; Ando and Dunn, 1999) effects of acute immune challenge share such similarity to major depressive disorder in humans that communication between the immune, nervous and endocrine systems has become a major focus of affective disorders research in general. For these reasons, immune dysfunction involving excessive macrophage derived cytokine production has in the past

been proposed a fundamental aspect of depression pathogenesis (Smith, 1991), and more currently, a role for cytokines in mediating depression-like neuro-behavioral changes in various somatic disease states is widely recognized (Dantzer, 2004).

Additional evidence from animal studies, however, provides reason to believe the relevant behavioral and physiological effects of cytokines are more comparable with the effects of stressors than with depression per se, given similarities in neuroendocrine changes that stressors and cytokines both can produce (Anisman et al., 2002a,b). Moreover, neurochemical effects of cytokines overlap to such a degree with those elicited by psychological (i.e., involving higher-order, sensory/cognitive processing) stressors that the brain appears to interpret and react to each as if they were the same (Anisman and Merali, 1999). Stressors clearly play a role in depression, particularly in situations where duration of exposure to

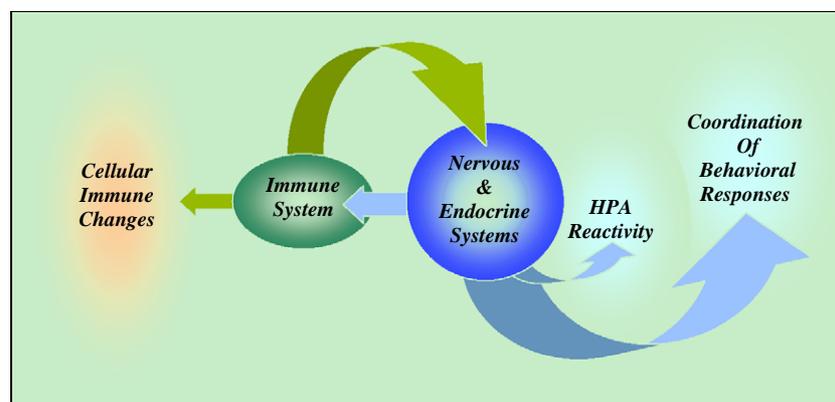


Fig. 1. Immune tissues are receptive to classic neurotransmitters and hormones; nervous and endocrine tissues are receptive to immune factors. Such interaction is the basis of much behavioral/neuroendocrine change associated with immune system activity, and physiological/immune system change associated with central nervous function.

them is chronic, and/or where physiological responses to them are disproportionately large (Chrousos and Gold, 1992, 1998; Claes, 2004). Taking into consideration the degree of overlap between effects of stressors and cytokines, the possibility that both similarly provoke depression is a compelling one. In line with this thinking, analogous to the manner in which regimens of chronic stress produce a depression-like syndrome in experimental animals (Willner, 1984; Willner et al., 1987, 1996), chronic administration of cytokines in a therapeutic context is well documented to produce a depression-like syndrome in humans (Capuron and Dantzer, 2003; Schaefer et al., 2003). Further, a number of studies have reported that a *single* stressor or immune challenge can result in lasting changes in vulnerability to affective illnesses by augmenting responses to subsequent insult (Anisman and Merali, 2003). In sum, like stressors, immune challenge appears capable of provoking a depression-like syndrome over a similar time course, by affecting the same systems, and by proactively influencing vulnerability to subsequent insult.

Nevertheless, there is clearly more to learn in terms of just how similar cytokines are to stressors in these respects, and furthermore, how short-term effects of cytokine exposure may be discerned from depression-like characteristics observed in experimental animal models. To address these issues, the body of this review will provide a summary of the literature on some of the short-term effects of acute immune challenge and stressors in rodents, along with some attention to specific mechanisms by which these effects take place. In addition, we will compare outcomes of immune challenge in typical rodent strains (e.g., Sprague–Dawley [SD], Wistar) against what is known in the context of clinical depression and depression models, including measures reported for the Fawn Hooded (FH) rat strain, an accepted animal model of clinical depression. Emphasis will be placed on comparative studies of biochemistry, behavior, and immune function between two genetically diverse animal models, i.e., one that is normal (SD) and one that is biochemically and immunologically compromised (FH). The purpose of this review is to illustrate how outcomes of immune challenge may differ depending on preexisting vulnerability to depression.

2. Presence of cytokines in the central nervous system

Many reports have confirmed the presence of cytokines and their receptors in several brain areas (e.g., hypothalamus, hippocampus [HPC], prefrontal cortex [PFC], and brainstem; Farrar et al., 1987; Katsuura et al., 1988; Araujo et al., 1989; Koenig, 1991; Lapchak, 1992; Schobitz et al., 1992; Ban et al., 1993; Haour et al., 1995), where concentrations are reported to fluctuate in response to a variety of insults (e.g., concussive brain injury, cerebral

ischemia, seizure, infection or endotoxin challenge, psychological stress; Licinio and Wong, 1999; Rothwell, 1999; Plata-Salaman, 2000; Rothwell and Luheshi, 2000; Reichlin, 2001). In situations where central function is affected, cytokines can be produced endogenously within the brain (Rothwell, 1999), or can gain access to the brain via circumventricular organs (Banks, 1999), by crossing the blood–brain barrier by altering cerebrovascular permeability (Ellison et al., 1990; Banks and Kastin, 1992), or else by recruiting peripheral immune cells into the brain, which may then express cytokines in turn (Proescholdt et al., 2002). In addition to direct influence on central targets, cytokines can also affect central function indirectly by stimulating peripheral vagal afferents (Maier et al., 1998; MohanKumar et al., 2000).

In later sections we will focus on studies that have reported the manner in which stressors and cytokines affect monoamines, serotonin (5-HT) and norepinephrine (NE), in the HPC. Given the central role HPC plays in sensory information processing, coordination of behavioral responses, and regulating HPA reactivity to stressors (e.g., Young et al., 1991; Herman et al., 2003), we feel the region serves well as an anatomical locus for examining possible cytokine-linked depression- and/or stress-like changes (Fig. 2).

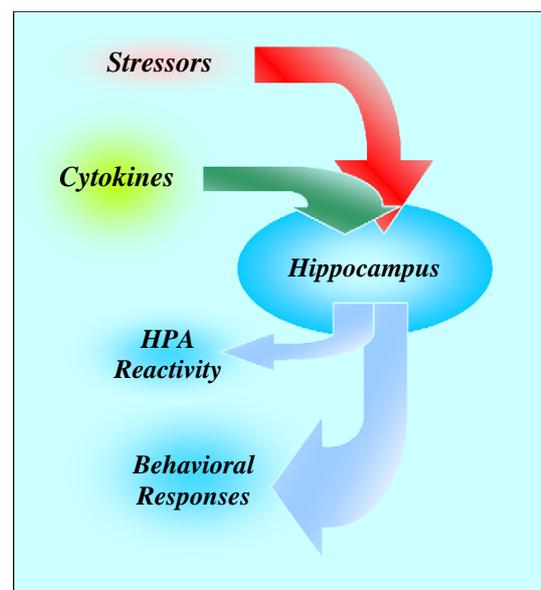


Fig. 2. The hippocampus (HPC) plays a central role in sensory information processing, coordination of behavioral responses, and regulation of HPA reactivity. Behavioral and physiological outcomes of stressor or cytokine challenge are very similar, and likely are mediated to some degree via the HPC. Underlying differences in HPC neurochemistry (e.g., 5-HT, NE) are revealed between animals that differ in vulnerability to depression. Pre-existing differences between animals (e.g., HPC neurochemistry), whether in-born, or resulting from previous exposure to stressor or cytokine challenge, may underlie differential reactivity of HPA output and behavior.

3. The Fawn-Hooded animal model of depression

The inbred FH rodent strain is an animal model of depression due most prominently to central and peripheral 5-HT abnormalities; 5-HT abnormalities are frequently associated with depressive disorders (Maes and Meltzer, 1995). Specifically, decreased concentrations of 5-HT in blood platelets (Tschoopp and Weiss, 1974), as well as decreased 5-HT and 5-hydroxyindoleacetic acid (5HIAA) concentrations in brain loci for cell body synthesis of 5-HT are found in these animals (Aulakh et al., 1994). Additional depression-like markers in the FH strain that involve central 5-HT include reduction in 5-HT agonist labeling in HPC and PFC (Hulihan-Giblin et al., 1992), abnormalities in 5-HT_{1A} receptor binding (Hulihan-Giblin et al., 1993; Chen and Lawrence, 2000), and blunted responses to centrally acting 5-HT agonists (Aulakh et al., 1988a,b; Wang et al., 1988). Other pharmacological evidence is based on NE dysfunction and provides support for the FH strain as an animal model of depression because, in human studies, depressed patients exhibit NE alterations; antidepressant medications are often designed to compensate for NE-ergic deficiencies (Baldessarini, 1989; Blier, 2001; Morrow, 2001). A specific parallel between clinically depressed patients (Charney et al., 1982; Lesch et al., 1990) and the FH strain (Aulakh et al., 1992) that involves NE transmission occurs in blunted growth hormone response to clonidine compared with control groups of nondepressed patients and normal animals, respectively. Important new evidence for NE deficiency in CA1 region of HPC in freely moving and behaving FH rats comes from neuromolecular imaging (NMI) studies using BRODERICK PROBE® sensors; the data show that basal NE release in FH animals are deficient by two-fold compared with normal, non-depressed SD rats (Broderick and Hope, unpublished data). Additional abnormalities in the FH strain related to depression include exaggerated immobility in the forced swim test (Overstreet and Rezvani, 1996) and elevated serum corticosterone (Aulakh et al., 1993), both of which are reversible via chronic antidepressant treatment (Rezvani and Overstreet, 1992; Aulakh et al., 1993).

In addition to central markers of depression, FH animals display differences in immune function compared to normal (e.g., SD) animals. We compared flow cytometric enumeration results of T-helper (CD4+) and T-suppressor (CD8+) splenocyte frequencies in SD and FH rats and the studies revealed a two-fold higher frequency of CD8+ in FH as compared with the SD strain. This shift in the frequency of CD8+ cells in the FH animals may well reflect an immune system which exhibits an incompatibility with normal homeostatic function (Coico and Broderick, unpublished data). It is interesting that such an incompatibility may also occur in HIV patients (Leserman et al., 2002) as well as in the elderly depressed (Castle et al., 1995). Given the caveat that immune function may differ between rodents and humans, in human depressed patients CD8+ frequency has

been reported to be lower, i.e., in depressed patients, the ratio of T-helper to T-suppressor lymphocyte population (CD4+/CD8+ ratio) is elevated with graded depression severity (Charles et al., 1992). Finally, there were no significant differences in T and B cell proliferative mitogen responses using untreated SD versus FH splenocytes cultured with concanavalin-A (Con A) or LPS. However, there remains the stipulation that such responses, as studied, tested only lymphoid functionality and did not test the capacity of either animal strain to display T cell functionality as regards cytokine production and/or B cell functionality as regards antibody production (Coico and Broderick, unpublished data). These differences in immune function are most relevant since immune dysfunction has been hypothesized to bear fundamentally on central and behavioral manifestations of depression (Smith, 1991) albeit depression-associated immune modifications may be secondary to depression-associated neuroendocrine changes (Tecoma and Huey, 1985). In another rodent model of depression (8 weeks of a chronic mild stress regimen, e.g., Willner, 1984; Willner et al., 1987, 1996), enhancement of IL-1 and IL-2 production by splenocytes, and enhanced Con-A mitogen responses were observed; importantly, these changes were reversible via antidepressant treatment (Kubera et al., 1996). More work is needed in which additional immune markers (e.g., aspects of cytokine function) implicated in clinical depression are examined in FH animals. Nonetheless, FH animals provide a viable experimental model in which to examine aspects of clinical depression.

4. Central and behavioral effects of cytokines and stressors in normal, “non-depressed” rat strains

4.1. Effects of cytokines and stressors on 5-HT release in HPC

There is considerable evidence that immune related factors affect the central transmission of 5-HT. It is important to point out, though, that effects among individual cytokines can differ depending on dose administered and functional outcome measured (Petitto et al., 1997; Pollmacher et al., 2002). Also, while non-specific immune activation via administration of bacterial endotoxin (e.g., lipopolysaccharide, LPS) is reported to enhance central 5-HT in rats (Lavicky and Dunn, 1995; Linthorst et al., 1995, 1996; Linthorst and Reul, 1998; Connor et al., 1999), the effects of cytokines are often receptor specific.

Receptor specific effects of cytokines are clearly present in the neurochemical changes they elicit within discrete regions of the brain; again, for present purposes attention will be focused on studies examining HPC. For example, in results published by Pauli et al. (1998), intracerebroventricular injection of IL-2 enhanced HPC 5-HT in Wistar rats, whereas injection of TNF α yielded no effect. Pauli and

colleagues further reported that effects of IL-2 injection come indirectly through IL-1 mechanisms, as pretreatment with a receptor antagonist for IL-1 (i.e., IL-1ra) prevented or attenuated the effect of IL-2 on HPC 5-HT. Pretreatment with IL-1ra was also found to attenuate induction of HPC 5-HT following peripheral injection of LPS (Linthorst et al., 1995). Other studies have confirmed the ability of IL-1 to increase HPC 5-HT in Wistar and SD strains (Linthorst et al., 1994, 1997; Merali et al., 1997; Broderick, 2002).

Data from several reports suggest that the effects of immune challenge on central 5-HT are mediated via the 5-HT₂ receptor subtype. As well, other centrally mediated effects of IL-1 or LPS injection in experimental animals (e.g., defensive rage, anorexia, REM sleep change) are 5-HT₂ mediated (Imeri et al., 1999; Hassanain et al., 2003a; von Meyenburg et al., 2003). Consistent with the hypothesis that IL-1 induction of 5-HT is mediated via the 5-HT₂ receptor subtype, 5-HT₂ receptors act in opposition to 5-HT_{1A} autoreceptors which, in addition to suppressing IL-1 elicited defensive rage and anorexia, diminish 5-HT transmission (Blanchard et al., 1993; Saphier et al., 1995; Cologer-Clifford et al., 1997; El-Haj et al., 2002; Hassanain et al., 2003b). Data from additional reports suggest that cytokines elicit these effects by acting directly on 5-HT terminals. Studies that have examined immediate early gene expression in response to peripheral LPS or IL-1 challenge report no detectable increase in c-fos mRNA in raphe nuclei (Elmqvist et al., 1993; Wan et al., 1993; Brady et al., 1994; Ericsson et al., 1994; Sagar et al., 1995). More evidence of action at 5-HT terminals is provided by findings that intra-HPC infusion of IL-1 results in local increases in extracellular 5-HT (Linthorst et al., 1994). Taken together, the effects of immune challenge, particularly IL-1, on central 5-HT appear to be mediated through the 5-HT₂ receptor subtype within 5-HT terminal regions.

Similar to the impact of immune cytokine challenge, microdialysis studies have shown acute stressor exposure also results in increased HPC 5-HT (Kalen et al., 1989; Pei et al., 1990; Kawahara et al., 1993; Thorre et al., 1997; Konstandi et al., 2000). An additional similarity to cytokines lies in the mechanism by which stressor effects are at least partially mediated. Specifically, stressor elicited behavioral changes (e.g., anorexia) appear to be mediated by 5-HT₂ receptors (Grignaschi et al., 1993; Papp et al., 2003), and are countered by the 5-HT_{1A} receptor subtype (Grignaschi et al., 1993; Shimizu et al., 2000). However, unlike immune challenge, acute stressors are demonstrated to increase the activity of raphe neurons (Bliss et al., 1972; Kennett and Joseph, 1981).

Both stressor and cytokine elicited increases in HPC 5-HT are in line with a role for this biogenic amine in neutralizing the central impact of destabilizing events (Kennett and Joseph, 1981; Kennett et al., 1985; Smelik, 1987; Cassano and D'mello, 2001; Lowry, 2002). Given the role of HPC in sensory information processing and regulating physiological reactivity to stressors (Herman et

al., 2003), normal 5-HT function in this brain region would appear crucial for maintaining central stability in the presence of insult, whether of psychological or of systemic (e.g., immune) origin. Overlooking any possible differences in magnitude of effects elicited by stressor versus cytokine exposure, there is little to suggest that cytokines are unlike psychological stressors in terms of their impact on HPC 5-HT in normal animals. Finally, the general effect of acute cytokine challenge in normal animals, which is an apparent increase in HPC 5-HT, is not what we might expect as a depression-like outcome because anti-depressant medications often enhance 5-HT transmission (Meltzer and Lowy, 1987; Curzon, 1988; Price et al., 2001). Indications of reduced 5-HT in severely depressed patients (Asberg et al., 1976) and in the FH animal model of depression (Tschopp and Weiss, 1974; Aulakh et al., 1994) reinforce this idea further.

4.2. *Effects of cytokines and stressors on NE release in HPC*

The central impact of immune challenge is also demonstrated by alterations in NE observed within a number of brain structures. Most frequently, studies have focused on the hypothalamus and have shown variable effects of immune challenge on NE release, including marked increases (Shintani et al., 1993, 1995; Connor et al., 1998; Linthorst and Reul, 1998), increased turnover (Zalcman et al., 1994), results that depend on the hypothalamic sub-region examined (MohanKumar et al., 1998; Brebner et al., 2000), or no effect at all (Merali et al., 1997). Fewer studies have examined the impact of immune challenge on HPC NE, and as reported for the hypothalamus, outcomes are somewhat conflicting. Linthorst and Reul (1998) demonstrated a modest increase in NE efflux within HPC elicited by peripheral injection of LPS to Wistar rats, whereas Merali et al. (1997) found no effect of IL-1 β in SD rats, and Broderick (2002) observed a modest but significant IL-1 α induced suppression in HPC NE in SD rats. Inconsistency of effects across studies may be accounted for by cytokine receptor specificity described earlier, and also by differences in route of administration; IL-2 was found to increase HPC NE upon intracerebroventricular injection (Pauli et al., 1998), while systemic administration had no effect (Lacosta et al., 2000).

Regarding the mechanism by which immune challenge affects central NE, LPS is observed to induce c-fos activation in locus coeruleus (LC) (Elmqvist et al., 1993; Wan et al., 1993; Sagar et al., 1995), which indicates a direct impact on NE cell bodies, though this is not found for all cytokines tested (e.g., IL-1 β , Brady et al., 1994; Ericsson et al., 1994). Alternatively, the impact of cytokines on central NE may come about via indirect means. Suppression of HPC NE is noted to occur simultaneously with increased HPC 5-HT in the same animals following IL-1 α injection (Broderick, 2002). It seems plausible that NE undergoes a compensatory reaction to 5-HT. Consistent with this

hypothesis, NE/5-HT interactions are documented to bear an inverse relationship, evidenced by data showing unit activity within LC is suppressed by 5-HT innervation (Gorea and Adrien, 1988), unit activity within raphe nucleus is suppressed by treatments that enhance NE release (Baraban and Aghajanian, 1980), and by data showing drug treatments that decrease HPC NE efflux simultaneously increase 5-HT release in the same region (Broderick, 1997).

Acute stressor exposure increases activity in LC neurons (Abercrombie and Jacobs, 1988; Valentino and Wehby, 1988; Valentino et al., 1998), and elevates HPC NE measured by microdialysis (Abercrombie and Jacobs, 1988; Kalen et al., 1989; Zhang et al., 1995). Elevated NE has been implicated in producing an enhanced state of arousal (Anisman and Zacharko, 1990), which is of adaptive significance where increased vigilance might be necessary for an animal to escape potentially life-threatening (i.e., stressful) situations. Considering that behavioral and/or physiological response to cytokines and infection often include increased sleep (Krueger and Toth, 1994; Krueger and Majde, 1995) which is of adaptive significance in its own right, one would suspect concurrent increases in central NE would be less consistently reported across brain regions implicated in behavioral vigilance, unlike reactions to psychologically stressful stimuli. This appears to be the case, at least for suppressed HPC NE observed following IL-1 α injection in SD rats (Broderick, 2002). Rather, NE suppression appears relatively depression-like in parallel with lower basal HPC NE observed in the FH depression model versus SD animals (Broderick and Hope, unpublished data). However, the IL-1 α induced suppression observed in SD animals being far less, at 25% below baseline, than the two-fold difference from baseline described between SD and FH strains, it remains to be determined whether suppression of this relative magnitude is appropriately characterized as a depression-like change in normal animals.

In any event, it is difficult to draw general conclusions with respect to the impact of immune cytokine challenge on HPC NE given the degree of inconsistency among studies, in addition to the likelihood that multiple factors (e.g., receptor specificity, route of administration, administration of cytokines during habituation or conversely during exploration) contribute to experimental outcomes. It is apparent, though, that the stressor effect on NE is more consistent across studies than is the cytokine effect on NE.

4.3. *Effects of cytokines and stressors on locomotor activity*

Suppression of spontaneous locomotor activity is a hallmark indication of behavioral depression in rodent models (Willner, 1984), and a frequently reported behavioral outcome of LPS challenge (Plata-Salaman and Borkoski, 1993; Kozak et al., 1994, 1995; Huang et al., 1999; Tollner et al., 2000; Engeland et al., 2001). The effect of LPS may be mediated via IL-1 and TNF α , which also

suppress locomotor activity when administered separately (Bianchi et al., 1992; Lacosta et al., 1998, 1999; Morgan et al., 2004). Consistent with these reports, IL-10 pretreatment blocks LPS stimulated production of IL-1 and TNF α from macrophages, and also suppresses locomotor effects of LPS challenge (de Waal Malefyt et al., 1991; Fiorentino et al., 1991; Dinarello, 1993; Moore et al., 1993). As for central effects described earlier, the impact of different cytokines on locomotor activity can vary. Whereas TNF α reduced spontaneous locomotor behavior as described by Bianchi et al. (1992), IL-1 α had no effect within the same series of experiments, and Broderick (2002) reported IL-1 α produced a tendency to increase locomotor activity in SD animals when measured during behavioral habituation.

As well as receptor specificity, other factors weigh in to account for variable locomotor effects of acute cytokine challenge. Pauli et al. (1998) reports differential locomotor effects of IL-2 and TNF α that depend on circadian cycle. In this work, locomotor activity was unaffected by IL-2 or TNF α during the light phase, but was suppressed during the dark phase of the circadian cycle. Others that have noted circadian effects also report an impact of sex differences on cytokine-linked changes in locomotor behavior (Engeland et al., 2003; Franklin et al., 2003). Disparity in effects reported between cytokines, or between studies for a given cytokine may further be accounted for by differences in behavioral paradigm, i.e., environmental familiarity may play a role. More specifically, behavioral effects of cytokine injection appear to vary depending on whether an animal is undergoing active exploration of a relatively unfamiliar environment, or is exhibiting a reduced level of overt responsiveness within an environment with which it has previously become familiar. In work by Broderick (2002) wherein cytokines produced a tendency to increase locomotor activity, SD animals received IL-1 α injection after spending 2 h in the testing environment, during the habituation period, whereas behavioral suppression was observed following cytokine injection when activity values were collected immediately upon animals being newly placed in an unfamiliar environment (e.g., Lacosta et al., 1998). This “environmental familiarity” effect appears critical to the outcome; it is consistent with behavioral studies from other laboratories as well (Svensson et al., 1986).

Stressor affects on locomotor activity also vary, but this appears to be contingent on the type of stressor to which animals are exposed. In general, suppressed locomotor activity is a frequently reported result of exposure to physical stressors (e.g., footshock; Katz, 1981; Van den Berg et al., 1998). In contrast, psychological stressors yield the opposite effect, an increase in locomotor activity (Van den Berg et al., 1998). Differential aspects of physical and psychological stressors are not unique in terms of effects on locomotor activity, but are also reported for impact on acquisition of cocaine and morphine self-administration (Kuzmin et al., 1996; Ramsey and Van Ree, 1993),

development of saccharine preference in tests measuring anhedonic effects of stressors (Pijlman et al., 2003), and for neurochemical changes in the nucleus accumbens (Marinelli et al., 2004). Herman and Cullinan (1997) proposed that differences between physical and psychological stressors may be accounted for by the manner in which they are processed. Specifically, physical stressors are suggested to gain relatively direct access to centers involved in triggering HPA outflow, whereas psychological stressors are more likely channeled through limbic (e.g., HPC) circuits. It is interesting then that some cytokines (e.g., IL-1 α) are capable of exerting direct actions on aspects of limbic circuitry in addition to HPA outflow. Thus, classifying behavioral outcomes of immune challenge may not be as simple as making distinctions between physical and psychological stressors. Furthermore, the circumstances under which behavioral measures take place must be carefully considered before drawing conclusions in this regard.

5. Effects of IL-1 α injection in the FH model of depression; comparison with the SD strain

5.1. Pre-existing vulnerability affects outcome of immune challenge

In summary of evidence reviewed thus far, in normal experimental animals, the neurochemical effects of acute cytokine challenge share much in common with those of stressors; in particular, the 5-HT-ergic effects of cytokines and stressors are remarkably similar. Fewer clear parallels exist between acute cytokine effects in normal animals and clinical depression, with the noted exception of suppressed HPC NE after cytokine challenge in experimental paradigms.

It is noteworthy that in normal animals, protracted effects of stressor (Bartanusz et al., 1993; Van Dijken et al., 1993; Johnson et al., 2004) or cytokine exposure (Tilders and Schmidt, 1998; Hayley et al., 2001; Anisman et al., 2003; Schmidt et al., 2003) are observed as cross-sensitization of systems in which a single prior exposure results in augmented reactions to subsequent insult. In this manner, psychological or systemic (i.e., immune) challenges may promote enhanced vulnerability to clinical depression, even in previously uncompromised animals. These sensitization effects of cytokines and stressors, and their possible relation to clinical depression pathogenesis have been well described in recent reviews (Anisman and Merali, 2003). But, preexisting vulnerability too affects outcome of acute immune challenge and there are little or no reports directly comparing an absence of preexisting vulnerability and a presence of preexisting vulnerability in terms of stress and/or clinical depression, although previous reports have indicated that age and past psychiatric history seem determinants of depression-like changes

over the course of chronic cytokine therapy regimens (Valentine et al., 1998; Capuron and Ravaud, 1999). For this reason, we will now focus attention on experimental paradigms which demonstrate dramatic differences in the acute and subacute effects of cytokine challenge between normal (SD) animals and animals that have vulnerabilities associated with depression (FH).

Briefly, the effects of systemically administered IL-1 α were observed in freely moving and behaving SD and FH animals. Within each animal, HPC (CA1 region) 5-HT and NE release were detected within seconds, separately and selectively, in real time, with BRODERICK PROBE[®] nano- and microsensors, using neuromolecular imaging (NMI) and a semidifferential voltammetric circuit (national and international patents: 1989, 1995, 1999 issued, 2002, 2004, pending). Uniquely, at the same time, locomotor and stereotypic behaviors were monitored with infrared photocell beams, thus providing an accurate and close cause-and-effect relationship between monoamines and behavior. Results of these experiments are summarized in Fig. 3.

5.2. Effects of IL-1 α exposure on 5-HT release in HPC: comparison of FH and SD animals

Within minutes following peripheral acute injection, IL-1 α significantly increased HPC 5-HT in both strains, though this occurred to a significantly lesser degree in FH animals. Notwithstanding previously mentioned deficiencies in the FH strain, the 5-HT biochemical pathway is apparently still capable of producing 5-HT, and further, of mounting a significant reaction to immune challenge not unlike central 5-HT reactions to stressors. Yet, the HPC 5-HT response to IL-1 α in the FH strain appears blunted relative to normal animals.

Subacute studies were also performed in both strains, 24 h later, with no further injection of cytokine and the dramatic differences in HPC 5-HT continued, within and between strains. It is interesting, given the relatively short half-life of the cytokine (Ramanathan, 1996), that the effect of injection on central 5-HT continued well beyond the completion of IL-1 α metabolism. This may indicate lasting, perhaps adaptive effects of immune challenge upon central mechanisms implicated in stress and depression. Continued deficiency in HPC 5-HT release in FH animals is likely associated with 5-HT deficiencies previously noted.

Given evidence that 5-HT modulates central reactions to stressors (Kennett and Joseph, 1981; Kennett et al., 1985; Smelik, 1987; Cassano and D'mello, 2001; Lowry, 2002), it seems reasonable to surmise HPC 5-HT deficiencies in the FH strain may be permissive of downstream physiological responses to insult, as noted in depression (e.g., loss of HPA feedback inhibition: Young et al., 1991). That is, because of 5-HT deficiencies, perhaps FH animals have a lower threshold for the initiation of activity in neuroendocrine and/or autonomic systems that promote changes relevant to affective disorders like depression. As mentioned earlier,

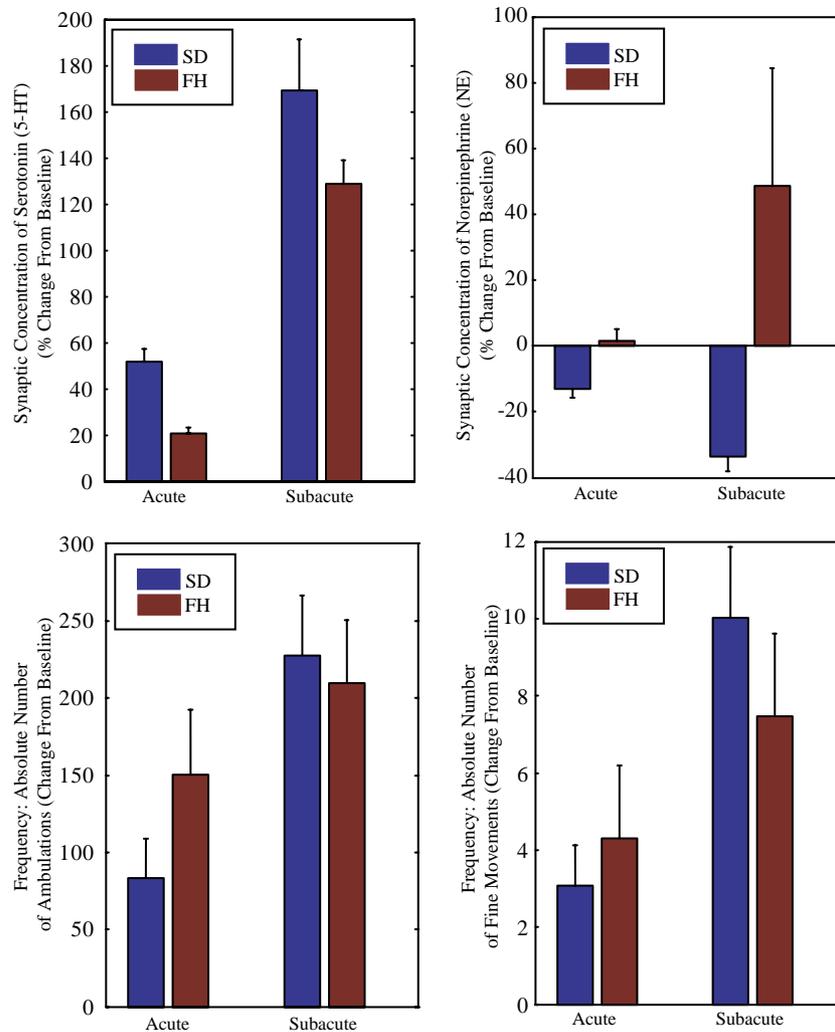


Fig. 3. Summary of results for comparison of Sprague–Dawley (SD) and Fawn Hooded (FH) strains in changes from baseline following peripheral injection of IL-1 α . Acute results reflect outcome following 100ng/kg injection of IL-1 α . Subacute results reflect outcome following 24 h, with no further cytokine injection (error bars=SEM).

others have argued that previous insult can cause protracted (e.g., neurochemical) changes in normal animals that leave them more vulnerable to affective illness (Anisman and Merali, 2003). Should biochemically determined 5-HT deficiencies contribute to depression vulnerability reported in FH animals, perhaps the protracted sensitization following cytokine or stressor exposure observed in normal animals is similarly based on 5-HT-ergic modifications. Nevertheless, cytokines would appear to contribute to affective illness at least in part by virtue of their ability to elicit lasting changes in sensitivity to subsequent insults in normal animals, and to trigger stressor-like reactions that are relatively augmented in vulnerable animals.

5.3. Effects of IL-1 α exposure on NE release in HPC: comparison of FH and SD animals

At a low dose, IL-1 α was found within minutes of injection to decrease HPC NE in SD and FH animals to a

similar and significant degree, but at a higher dose, a dramatically different pattern of effects was observed between strains. In SD animals, the higher dose produced an additional modest decrease in HPC NE, while in FH animals NE rebounded, and rose above baseline values.

Subacute effects of the cytokine on HPC NE also differed vastly between strains. Whereas SD animals displayed a further significant decrease below baseline, a significant, continued increase in NE release was observed in FH animals. As previously noted, given the relatively short half-life of IL-1 α , adaptive effects of immune challenge on central mechanisms may be held to account for relatively long-term alterations in HPC neurochemistry. An additional possibility is, again, that the increase in HPC NE continues due to a lack of compensatory suppression via 5-HT in FH animals. More generally, it seems likely that differences in the initial status of the systems affected between strains account for differing outcomes, with the added consideration that changes

elicited by cytokines are rather labile, prone to vary in form and magnitude over time (Schmidt et al., 1995; 2003). Regardless, measures of HPC NE in SD and FH animals provide further indication of lasting, perhaps adaptive effects of immune challenge upon central mechanisms implicated in stress and depression.

The difference between strains for HPC NE found at the higher IL-1 α dose provides further indication that FH animals are especially prone to physiological changes typically associated with stressors (e.g., elevated HPC NE, Abercrombie and Jacobs, 1988; Kalen et al., 1989; Zhang et al., 1995). What is more, measures of HPC NE in the FH strain are reminiscent of changes elicited by chronic stressor regimens that produce depression in normal animals. Analogous to the effect seen following IL-1 α challenge in the FH strain, SD animals previously exposed to chronic cold water immersion display significantly elevated and prolonged HPC NE release in response to a novel stressor, compared to reactions observed in naïve rats (Nisenbaum et al., 1991; Nisenbaum and Abercrombie, 1992). Similar “stress-induced sensitization” is noted for PFC NE (Gresch et al., 1994; Finlay et al., 1997), as well as for systems mediating other responses that are relevant to stress and depression (e.g., HPA outflow, Bartanusz et al., 1993; Van Dijken et al., 1993). With respect to the inverse regulatory relationship suggested earlier between 5-HT and NE, it is possible blunted 5-HT in FH animals permits a relatively large NE response to insult of psychological or immune origin. In sum, central NE reaction to IL-1 α injection in FH animals appears to be rather stressor-like and to reflect an exaggerated sensitivity to insult. This further illustrates how outcomes of immune challenge can vary depending on varying degree of preexisting vulnerability across animal models.

5.4. Effects of IL-1 α exposure on open-field behavior: comparison of FH and SD animals

The effects of IL-1 α observed in movement behaviors (e.g., ambulation, stereotypic sniffing and grooming) were episodic in both strains; this was more readily apparent in FH animals. There was an apparent tendency toward an increase in locomotor activity in both strains following acute injection. Interestingly, locomotor counts were higher in FH versus SD animals, though this may have resulted in association with the episodic nature of the behavioral outcome. Stereotypic sniffing and grooming behaviors also increased in both strains. Again, there was a tendency for stereotypic sniffing and grooming to be increased in FH versus SD animals.

The subacute effects of IL-1 α injection were observed as significant increases in locomotor activity in both strains versus baseline; no significant difference was observed between strains. Stereotypic sniffing and grooming was again increased in SD and FH animals versus baseline, though there was no significant difference between strains.

Described earlier, a tendency toward increased behavioral responsiveness within a previously habituated to environment may indicate stressor associated mechanisms are in play (e.g., increased vigilance). With respect to the effects of injection, the difference between strains in the acute study provides an additional example of how animals with preexisting biochemical vulnerabilities associated with depression express augmented stressor-like reactions to immune challenge. The subacute results are more difficult to resolve, though again this may be accounted for by potential differences in the initial status of systems affected in each strain, the labile nature of cytokine effects over time, and the episodic nature of these behavioral responses following injection. Nevertheless, it appears most likely that differences in reactions between strains to IL-1 α injection indicate FH animals are more sensitive in terms of stressor-like outcome.

5.5. Effects of IL-1 α exposure on immune cell mitogenic responses: comparison of FH and SD animals

In addition to relatively direct central and/or behavioral effects, stressor- or depression-like outcomes of a given insult may occur indirectly via a cascade of cellular immune events (e.g., stress associated increases in T-cell mitogen responsiveness and cytokine release: Kubera et al., 1996). For this reason, it was of interest to examine effects of cytokine injection on aspects of immune function between rodent strains. In our laboratories we examined T cell proliferative mitogen responses in spleen cells from rats injected with IL-1 α . There was a profound difference between strains in the initial acute response in that measures obtained for the FH strain were significantly higher (two-fold) than those observed from SD animals. Although no change occurred in the B cell subset, a significant change in the T cell mitogen response indicates in the FH strain that there may be an incurred hypersensitivity following cytokine challenge, i.e., an augmented responsiveness to cytokine challenge in the FH strain compared with the SD strain. The finding suggests that the IL-1 α mediated cascade of immune events is potentiated in FH versus SD animals, wherein the magnitude of inflammation may be relatively pronounced (Coico and Broderick, unpublished data). Therefore, regarding the differential effects of IL-1 α on mitogen responses between SD and FH animals, it would appear that in addition to augmented behavioral and neurochemical stressor-like effects noted in FH animals, there is evidence to suggest augmented responsiveness to IL-1 α in aspects of cellular immunity.

The subacute effects of IL-1 α were less dramatic, though there was still a tendency for T cell mitogen responses to be elevated in FH versus SD animals. The difference in magnitude between acute and subacute effects may correspond with the short half-life of the cytokine. As well, differences between acute and subacute effects may be accounted for by the lability of cytokine effects over time, as

observed for behavioral and neurochemical measures described earlier.

6. Conclusions

Evidence reviewed here suggests that cytokines, much like psychological stressors, are capable of provoking physiological changes implicated in depression, and of promoting greater vulnerability to depression that becomes manifest upon subsequent exposure to insult. Furthermore, evidence that FH animals, like normal animals previously exposed to stressor or cytokine challenge, show augmented behavioral and neurochemical reactions to IL-1 α injection provides greater validation for models of depression pathogenesis that are based on the protracted effects of acute psychological or systemic insult (Fig. 4). The additional finding, that IL-1 α pretreatment enhanced mitogen responses in FH more so than in SD animals, provides evidence to suggest immune function is compromised during depression. However, there remain questions as to whether basal immune differences in FH animals are purely of collateral nature should depression be driven fundamentally by abnormal neuroendocrine function, or whether, to any degree, immune dysfunction contributes more fundamentally to observed neuroendocrine changes (i.e., via excessive release of cytokines). Regarding the short-term impact of immune challenge, despite any degree of overlap between cytokine effects and basal measures

noted for clinical depression and depression models described presently, the changes elicited do not seem a sufficient characterization of depressive disorder per se. More work is needed where effects of relatively chronic (i.e., >7 days) regimens of cytokine exposure are implemented in experimental animals, given that in natural situations where cytokine levels are altered, the changes are rather persistent by comparison to most experimental models previously reported. Furthermore, the changes observed in humans over the course of cytokine immunotherapy may be unique to that clinical situation, and effects of relatively short-term cytokine treatment in experimental models, too, may be limited in interpretation.

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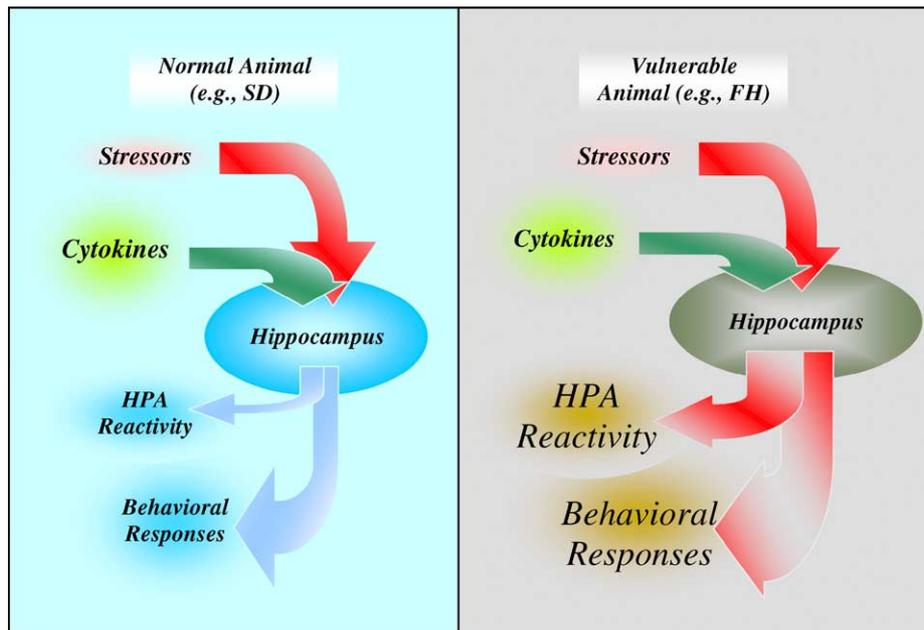


Fig. 4. Given the central role the hippocampus (HPC) plays in sensory information processing, coordination of behavioral responses, and regulating HPA reactivity to stressors, abnormal behavioral and physiological outcomes of stressor or cytokine challenge likely correspond in an animal within which HPC neurochemical abnormalities are present. Underlying differences in HPC neurochemistry (e.g., 5-HT, NE) revealed between strains that differ in vulnerability to depression (e.g., SD vs. FH) may contribute to differential HPA outflow and behavior, as well as other concomitants (e.g., mitogen activity, CD4/CD8 ratio) which may be affected secondarily. Differences between SD and FH animals are evident in neurochemical, behavioral, and immune reactions to IL-1 α injection.

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