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Impact of superantigenic molecules on central nervous system function

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1. ABSTRACT

Superantigens (SAgs) activate the immune system by stimulating massive proliferation of T cells in a major histocompatibility complex (MHC)-dependent manner. This excessive increase in T cells results in the release of cytokines such as interleukin-2 (IL-2), interferon-gamma (IFNγ), and tumor necrosis factor-alpha (TNFα). As an adaptive feedback mechanism, SAgs can also activate the hypothalamic pituitary adrenal (HPA) axis by stimulating the release of corticotropin releasing hormone (CRH) from the hypothalamus, adrenocorticotropic hormone (ACTH) from the anterior pituitary, and ultimately corticosterone (CORT) from the adrenal gland. Additionally, SAg exposure modifies behavior, although it has not been shown to induce malaise or decrease mobility. Some behavioral consequences include increased gustatory neophobia, neophobia to inanimate non-gustatory objects, and heightened anxiety. Cytokines such as TNFα have been shown to mediate some of these behavioral consequences as well as the endocrine and neurobiological effects of SAg exposure. The particular behavioral repertoire and cytokine profiles observed are in some cases unique to SAgs, as compared to other immune challenges such as lipopolysaccharide (LPS). Therefore, SAgs serve as a useful model to understand the behavioral, endocrine, and neurobiological effects of a T cell driven immune response.

2. INTRODUCTION

Superantigens are potent immunologic stimuli that originate from bacteria and viruses (1, 2), and possess the capacity to stimulate in an MHC-dependent manner up to 10-20% of all T cells in a given host (3). This major recruitment of T cells is independent of clonal specificity, and results in substantial proliferation and cytokine production (4, 5). Of note is that the circulating concentration of cytokines (eg., IL-2, IFNγ and TNFα) achieves easily detectable levels, far exceeding the capacity of regular, benign protein antigens (eg., hemocyanin) to generate similar amounts that can be detected *in vivo* without resorting to limiting dilution procedures (6). The latter is a reflection of the lower frequency of T cell recruitment, but does speak to the potential clinical impact that SAgs can exert on the host by virtue of committing so many more T cells into a cytokine-producing state. That is, as a systemic condition, exposure to superantigenic molecules can pose considerable risk due to the sustained production of cytokines that are normally tightly regulated to prevent excessive inflammation and immunopathological disease. For example, it has been well established that exposure to SAgs can result in shock and increased mortality (7), with some suggestions also being made that SAgs can promote increased vulnerability to autoimmune responses (8, 9). Therefore, the extraordinary nature of the

T cell response to SAg molecules poses a considerable threat to health.

Given the protective nature of the immune response to infectious pathogens, it is unusual that in the case of SAgs, the immediate response bypasses the basic tenets of adaptive immune reactivity, such as antigen processing and peptide presentation to T cells, with associated promotion of B cell antibody responses and T cell cytotoxicity. Typically, this canonical progression of the adaptive immune response takes place over a 24-48 hr period prior to the appearance of antigen-binding antibody responses. However, the unique nature of the SAg stimulation of the T cell receptor results in alternate consequences of massive proliferation and cytokine production in a matter of hours (10). The protective function of this response has remained elusive, while the suggestion that it benefits more the pathogen producing the toxin, rather than the host, has not been empirically tested (7).

Superantigens were first identified by Marrack and Kappler (11-13), with the largest number attributed to the gram positive bacteria *Staphylococcal aureus and Streptococci* (1, 2). Of these, the best characterized are the staphylococcal enterotoxins, for which an appreciable amount of information exists in terms of their ability to stimulate specific subsets of mouse, rat and human T cells (14-17). In addition, SAgs have been identified for B cells (18), although much of the present discussion will focus on T cell superantigens. The "superantigenic" properties of these agents is a reflection of their ability to stimulate 10^4 fold more T cells than conventional antigens. The term antigen refers to any stimulus that initiates an immune response, and has the capability of inducing the production of antibodies. In so far as the latter is typically dependent on the cooperation of T cells, most antigenic molecules engage T cells subsequent to processing and MHC-dependent presentation by antigen-presenting cells (eg. dendritic cells). This is achieved in a clonally specific manner, such that the inner peptide-binding groove of the T cell receptor is the site for specific recognition of the multitude of different antigenic determinants (or epitopes) that can be presented by MHC molecules. Therefore, for each peptide sequence representing an epitope of some larger protein antigen, there exists a given T cell clone whose TCR recognizes that particular epitope. The net result of this specificity is that of the entire pool of mature T cells in a mammalian organism, the frequency of responsiveness to epitopes from processed proteins derived from foreign sources (eg., bacteria or viral envelopes) is estimated to approximate 0.002% (3). Therefore, the considerably greater number of T cells stimulated by SAgs represents an extraordinary activation of the immune system, and consequently higher levels of cytokine production. This over abundance of circulating cytokines may have a profound impact on biological functions, including those of the central nervous system.

The abundant numbers of T cells activated by SAgs is therefore a reflection of oligoclonal stimulation, and reflects the selectivity of SAgs for unique motifs on the variable region of the TCR beta chain (Vβ) (11-13). However, the molecular characteristics of superantigenic stimulation of T cells are best understood in terms of the recruitment of T cells carrying specific Vβ genes (e.g., Vβ1, Vβ2, Vβ3 etc; and see Proft & Fraser, 2003 for a detailed description)(2). Briefly, relatively invariant amino acid sequence motifs can be present on multiple clonally-specific TCRs that are encoded by the same Vβ gene. The net result is that T cells bearing clonal specificity towards different antigenic peptides, can still be categorized according to the same Vβ gene coding for this common, invariant motif on the TCR. Consequently, T cells can be classified, say, as $V\beta3^+$ T cells, and still be further differentiated according to their responsiveness to different antigenic peptides (19).

2.1. Staphylococcal Enterotoxins

Perhaps the greatest understanding of the immunological effects of SAgs has come from studies of the secreted toxins of *Staphylococcal aureus*, a gram positive bacteria long recognized as a major pathogen responsible for infections and food poisoning (20). The major exotoxins of *S.aureus* have been classified as cytotoxins, pyrogens, and exfoliative toxins, with the superantigenic toxins falling into the pyrogenic class (21). This includes the staphylococcal enterotoxins (SEs) and toxic shock syndrome toxin (TSST). With regard to the SEs, serological distinctions have been made, with each toxin coded by separate genes, and with some amino acid homology found across different toxins (21). These variations are reflected by the application of an alphabetic nomenclature for the SEs (viz., SEA [for staphylococcal enterotoxin A], SEB, SEC, and so on), with some being further categorized into subtypes (eg., SEC_1, SEC_2 and SEC_3). Indeed, as reported in previous reviews, at least 15 different SEs have been identified along with their Vβ specificity (22, 23). Analysis of this Vβ specificity has revealed considerable heterogeneity in their affinity to the full range of known Vβ genes in a number of different species including human and non-human primates, as well as rats and mice (23). In mouse studies, it is important to note that the relative percentage of T cells bearing any one particular member of the Vβ family can differ between inbred mouse strains. This can result in variations in the composition of T cells bearing different Vβ phenotypes in mice exposed to particular SEs (24). For example, many studies have used C57BL/6 and BALB/c mice, and in these strains, the magnitude of T cell reactivity varies according to which Staphylococcal SAg has been administered. Therefore, it is commonly observed that in BALB/c mice, exposure to staphylococcal enterotoxin B (SEB) will preferentially engage Vβ8 T cells, whereas in C57BL/6 mice these cells are not as readily recruited; alternatively, injection of C57BL/6 mice with SEA produces marked activation of Vβ3 T cells. These biases and the ensuing dramatic effects on cytokine production have been exploited by different investigators, resulting in good evidence that SEA and SEB produce neurobiological and behavioral effects, as summarized in Table 1, and further discussed in the remainder of this paper (25).

Table 1. Summary of major biological, endocrine, and behavioral properties of superantigens

T cell stimulation	• Antigen processing independent • T cell dependent • MHC dependent • 10^4 more T cell stimulation than conventional antigens
Cytokine Production	↑ IL-1, IL-2, IL-6, IL-10 ↑ IFN-gamma ↑ TNF-alpha
HPA axis activation	↑ CRH ↑ ACTH ↑ CORT
Behavior not severely affected	• Mobility • Malaise
Behavior affected	↑ Gustatory neophobia ↑ Neophobia to novel object ↑ Exploration of EPM

3. SUPERANTIGENS AND THE HYPOTHALAMIC PITUITARY ADRENAL (HPA) AXIS

As noted earlier, the staphylococcal enterotoxins are classed as pyrogenic toxins, which in and of itself, suggests the activation of central thermoregulatory brain systems, such as those controlled by the hypothalamus. Indeed, it has been demonstrated that rats injected with SEB show febrile responses, which was pursuant to an initial activation of hypothalamic neurons, as well as elevations in plasma corticosterone (26). Corticosterone is a glucocorticoid produced by cells of the adrenal cortex, and has long been regarded as an endocrine measure of physiological and/or psychological stress (27). Additionally, elevations in corticosterone are generally a result of upstream activation of the hypothalamic-pituitary axis which results in the release of ACTH, the pituitary hormone responsible for the adrenocortical release of glucocortioid hormones (27). The observation of increased corticosterone release in response to SEB administered to rats (26) was an extension of earlier work in mice first reported by Gonzalo *et al* (1993). This latter study demonstrated in C57BL/6 and BALB/c mice that challenge with SEA or SEB could elevate plasma concentrations of corticosterone, an effect that was essential for survival, since adrenalectomy or glucocorticoid receptor antagonism resulted in increased mortality (28). In this regard, it was clear that glucocorticoid responses to bacterial SAgs were a critical adaptive feedback mechanism, as has been shown in the endotoxin (or LPS) shock model (29, 30). These observations of SEB-induced corticosterone release were corroborated in the context of studies investigating steroid regulation of T cell apoptosis (31), but without determining whether central mechanisms were driving the elevations in corticosterone. This latter issue was addressed by Shurin *et al* (1997) who found in BALB/c mice that the elevated corticosterone response to SEB was associated with ACTH production (32). This effect of SEB on the corticosterone response has consistently been demonstrated in rats and mice (33, 34).

To the extent that concordant changes in ACTH and corticosterone constitute evidence for activation of the pituitary-adrenal axis, this suggested the activation of neurally controlled ACTH secretagogues, such as corticotropin releasing hormone (CRH; aka CRF) and arginine vasopressin (AVP) (35). The plausibility of upstream neural events being involved in increased pituitary-adrenal activation was provided by evidence for SEB induced activation of the paraventricular nucleus (PVN) of the hypothalamus, as measured by immunohistochemistry and *in situ* hybridization for the immediate early gene, *c-fos* (26, 36, 37). In contrast, a more recent study, found that exposure of rats to SEB did not produce an appreciable activation of the PVN (38). However, this latter study did observe elevated plasma concentrations of corticosterone and ACTH, as well as central activation of other brain regions important to emotional regulation. Moreover, in mice it was found that challenge with SEB not only elevated corticosterone levels, but also increased norepinephrine levels, suggesting activation of the sympathetic nervous system (34), which is associated with increased activation of the PVN (34, 39).Consequently, at least for SEB, the bulk of the evidence in rats and mice is supportive of a central basis for the stimulatory effects of this SAg on pituitary-adrenal hormones.

In addition to SEB, another staphylococcal superantigen, SEA, has been shown to produce activation of the HPA axis. In the original report by Gonzalo *et al* (1993) injection of C57BL/6 mice with SEA increased plasma corticosterone. This was confirmed by Shurin *et al* (1997), this effect being associated with elevated ACTH (40). Additional investigations showed that the pituitary-adrenal effects of SEA occurred at a minimum dose of 1 μg per mouse (approx. 40 μg/Kg), with a peak elevation of plasma corticosterone measured at 2 hrs (41). Interestingly, in the same study, administration of SEB to C57BL/6 mice produced a modest increase in plasma corticosterone; however, this was relatively short-lived, but suggested that the small proportion of Vβ8+ T cells in the C57BL/6 mouse could be stimulated by the appropriate SAg to produce a neuroendocrine effect.

It should be noted that most studies on the effects of SEA or SEB on HPA axis activation have assessed hormone levels after only a single injection. Generally, in cases such as endotoxin (i.e. LPS) challenge, it is difficult to assess the neurobiological effects of repeated challenges since an immunologic form of tolerance develops, and which accounts for a loss in corticosterone elevations to LPS (42). Similarly, in the case of SAgs, and in particular SEA and SEB, repeated exposures can result in T cell anergy (28). Since nothing was known about the corticosterone response after repeated injections of SEA, a recent study with C57BL/6 mice (43) administered SEA up to four times at intervals of 3-5 days. In contrast to studies with LPS, it was found that the corticosterone response to SEA was still evident in response to the third injection, although by the fourth challenge this was no longer the case (43). In an unpublished observation, the corticosterone response of BALB/c mice to a second injection of SEB was still evident when the toxin was administered 7 days after the first (unpublished observations, Kusnecov laboratory). In summary, there appears to be little dispute that SEA and SEB activate the pituitary-adrenal axis in mice and rats, and that this can be reenlisted with repeated exposures to these SAgs.

It had been established some time ago that SEA and SEB stimulate T lymphocytes through co-dependent binding to MHC Class II molecules (11, 12). However, some evidence also exists that Staphylococcal enterotoxins stimulate non-T cells (44, 45), and this may be relevant to the pituitary-adrenal effects of SEA and SEB. However, it was shown earlier that athymic nude mice, that lack mature T lymphocytes, failed to show a corticosterone response following SEB injection (31); on the other hand, the corticosterone response became evident if mice were reconstituted with T cells, suggesting a dependence on the presence of functional T cells capable of responding to SEB (ibid). Pharmacologic suppression of T cell function using cyclosporine was also shown to inhibit the corticosterone response to SEB (32), but not to SEA (41). In both cases, cyclosporine completely suppressed T cell proliferation and IL-2 production, and also did not affect the ability of LPS (a predominantly monocyte/macrophage stimulus) to activate the pituitary-adrenal axis (32). Moreover, in the case of SEB-treated BALB/c mice, depletion of macrophages did not affect the corticosterone response (ibid). Consequently, in the case of SEA the results suggested that non-T cell mechanisms may be responsible for increased corticosterone levels. However, an additional experiment using T cell deficient Rag-1 knockout mice failed to induce a corticosterone response to SEA, but not to LPS (41). Therefore, while the cyclosporine results for SEA remain perplexing, there appears to be good evidence that the corticosterone-elevating effects of SEA and SEB require the presence of mature and functional T cells.

3.1. The Role of Corticotropin-Releasing Hormone (CRH)

Pituitary ACTH release is under the influence of various neuropeptide hormones, including CRH and AVP. The relative primacy of these peptides in their effects on ACTH release varies under different stress conditions, although it is generally agreed that in response to acute stressors, CRH is the main peptide driving ACTH secretion (46-48). In contrast, the contribution of AVP appears to be incorporated during chronic stress conditions (49, 50). It has been known for some time that immunologic stimuli activate the HPA axis, which ultimately led to confirmation that central CRH release was associated with pituitary-adrenal responses to cytokines, such as interleukin-1 (51). In addition, the ACTH response to an injection of LPS was shown to be attenuated by CRH receptor antagonism (52).

As in the case of endotoxin and IL-1 challenge, a number of studies suggest that in mice, CRH may be involved in the effects of acute SAg injection on HPA axis activation. Mice challenged with SEB showed increased CRH mRNA levels in the PVN and central nucleus of the amygdala, and immunoneutralization of CRH significantly reduced the ACTH response to SEB (53). Similarly, since pituitary ACTH-secreting cells express the R1 subtype of CRH receptors (52), mice challenged with SEA were systemically administered the selective CRH-R1 antagonist, astressin; the results showed a significant attenuation of the corticosterone response to SEA (54). These data demonstrate that the full extent of the HPA axis is activated by SAg administration, with initial recruitment of CRH producing neurons in the PVN serving as the initial stimulus within the neuroendocrine system. However, this conclusion applies to responses induced by acute SAg injections. As noted earlier, it has been documented that the corticosterone response to SEA continues to be evident after 2-3 injections (43). Additional information is required as to whether this increase in corticosterone is dependent on CRH on each occasion of repeated SEA exposure, or whether recruitment of other ACTH secretagogues is involved. Indeed, it has been noted that the initial early phase of the pituitary-adrenal response to a single LPS injection is dependent on the AVP 1b receptor (46). Whether a similar early dependence on AVP occurs after SAg injections remains to be determined.

4. EFECTS OF SUPERANTIGENS ON BEHAVIOR

There is now a large literature on the behavioral effects of immunological activation, which has led to the concept of 'sickness behavior' as a behavioral syndrome emerging from cytokine-induced activation of the CNS (55). The behavioral changes observed are typical of organismic reactions to stress, and generally reflect anorexia, anhedonia, impaired somnolence, and disruption of cognitive processes (55, 56) and may represent the alignment of behavioral goals with the effector state of the immune system. For example, removal of pathogens by immunological cells and antibody requires a general systemic adjustment which includes not only increased endocrine activity but also restriction of behaviors that otherwise would compromise neutralization and elimination of infection.

Indeed, increased activation of the HPA axis has been hypothesized to regulate ongoing immune responses (57), and it is well known that higher-order neural structures that provide afferent input to the hypothalamus are involved in controlling ingestive, emotional and cognitive processes. Through immediate early gene mapping studies (eg., c-Fos immunohistochemistry), it has been confirmed that such areas include not only the cortex and hypothalamic nuclei, but also the hippocampus, septum, bed nucleus of the stria terminalis, and amygdala, in addition to central autonomic nuclei, such as the locus coeruleus and nucleus of the solitary tract (58, 59). Consquently, while animals may display inhibited movement and exploration, there is little reason to suspect that sickness behavior reflects a suspension of cognitive and emotional processing. Surprisingly, mice acutely administered bacterial SAgs intraperitoneally do not show overt evidence of malaise, such as piloerection and diarrhea (unpublished observations, Kusnecov laboratory), although in rat studies, pyrogenic effects have been observed (26). In contrast, enteric delivery of staphylococcal enterotoxins or injection in the presence of D-galactosamine, a liver toxin, will produce malaise and/or septic shock and increased mortality (5, 60, 61). These latter experimental manipulations are unique or do not correlate with T cell activation, and are therefore difficult to relate to those studies reporting CNS effects after bolus intraperitoneal injections of SEA or SEB in the absence of any further

treatments (eg., d-galactosamine). In the studies already discussed showing HPA axis activation, SEA or SEB treatment increases circulating IL-2 and TNFα, but does not affect mobility nor subsequent 24 hr body weight loss, which stands in contrast to a reduction in the ingestion of food other than that normally provided in the home cage (viz., regular laboratory chow) (53, 54). However, if animals were preexposed to the irregular food (liquid diet or commercial food pellets) the SAg-induced hypophagia (or anorexia) was significantly attenuated (41, 53, 54). These manipulations were designed to test the neophobic reactions of the animals to novel food, and suggested that the T cell response to SEA or SEB augments food neophobia. Furthermore, after familiarization with a given food in an operant chamber where nose-pokes deliver food pellets, there was no disruption of performance nor ingestion of food pellets in response to SEA treatment (Kusnecov laboratory, unpublished observations). Therefore, acute systemic injections of staphylococcal enteroxins at minimal doses that activate the HPA axis do not produce dramatic signs of malaise that might otherwise lead to an interpretation of anorexic behavior due to illness or motoric impairment.

Further assessment of behavior following SAg challenge has revealed enhanced neophobia in the presence of inanimate, non-gustatory objects (41). An open field-novel object test was used, since it was demonstrated to be an index of anxiety-like behavior in mice (62, 63). Animals were observed initially exploring an empty open field environment, after which an unfamiliar cylindrical object was placed in the central region of the field. As reported by Kawashima and Kusnecov (2002), there was no impact of SEA challenge on exploration of the open field, which was in keeping with points made earlier concerning the absence of frank malaise and continued maintenance of motor behavior. However, the introduction of a novel object, resulted in greater arrest of ongoing behavior and physical interaction with the object in SEA treated animals. This likely reflected increased anxiety and/or neophobic behavior (41), and provided additional evidence, that as shown later for SEB, there is no fundamental suppression of locomotor behavior, unless provoked by novel stimuli (41, 64).

It was thought that the suggestion of increased anxiety-like changes produced by the novel object test in SEA treated animals could be generalized to other more traditional tests of anxiety-like behavior. One such test is the elevated plus maze (EPM), long considered as a useful index of modified anxiety state in rats and mice. However, it was paradoxically observed that when C57BL/6 and BALB/c mice were challenged with SEA or SEB, respectively, exploratory behavior was in the direction of less, rather than more, anxiety (64). That is, animals showed greater preference for entering the open arms of the EPM, which is generally interpreted as a sign of reduced fear/anxiety. Further testing for anxiety-like behavior in the light-dark box, another commonly used test of anxiety (65), failed to show any influence of SEA or SEB treatment. For example, administration of SEB to male BALB/c mice did not affect latency to exit from the dark compartment, nor the number of light–dark transitions and total time spent exploring the illuminated arena (64). Interestingly, in the EPM, BALB/c mice given SEB spent more time spent in the open arms, which at least demonstrates a behavioral effect otherwise unseen in the light-dark box test. It should be acknowledged, however, that the light–dark box and EPM may not assess similar underlying "emotional" processes (66), since the stimulus conditions of each test are different, and may not be engaging and/or interfering with relevant neurobiological processes that one might be attributable to anxiety-like states. For example, while the increased open arm exploration due to SEA or SEB treatment might otherwise suggest less "anxiety," an alternative interpretation could easily attribute this behavior to increased impulsiveness. Such an interpretation is highly speculative, however, and indeed raises an important problem regarding what constitutes "anxiety" in these tests. This problem is compounded by the failure of others to successfully identify anxiety-like behavior in the EPM or light-dark box following ostensibly anxiogenic treatments, as discussed elsewhere (64). Nonetheless, the range of behavioral assessments that could be conducted on animals treated with SEA or SEB has not been fully exhausted, since nothing is known at present concerning cognitive behaviors, and within this category, learning and memory. However, at the very least, perhaps the most reliable change is that of reduced food intake, and therefore, has been used to determine the central and peripheral mechanisms by which SEA exerts its effect on behavior.

4.1. Role of CRH

Contextual novelty can alter the quantity of food and/or water consumed, and this has been shown to be CRH-dependent, since this highly versatile peptide has long been regarded as anxiogenic (67). However, the arousing or anxiety-regulating properties of CRH are considered the result of differential engagement of two major CRH receptors, CRH-R1 and CRH-R2 (68). The anxiogenic effects of CRH are believed to be mediated by CRH-R1(48) , which was also shown to be the mechanism by which SEA injection led to increased pituitary-adrenal activation. As for the anorexic effects of CRH, either receptor may be involved, although the hypophagia measured may be mediated by increased arousal or a non-arousal based inhibition of food ingestion, where animals simply fail to show a motivation to consume food. Therefore, it was proposed that CRH-R1 mediated anxiety-based suppression of food intake, whereas basic appetite regulation occurred through CRH-R2 (69). Moreover, while CRH showed greater selectivity for CRH-R1, CRH-R2 was shown to be more selectively engaged by the more recently discovered peptide, Urocortin (UCN) (69).

A test of which CRH receptor mediated the effects of SEA on food intake in a novel situation was assessed by Kaneta and Kusnecov (2005), using two different CRH receptor antagonists administered intracerebroventricularly. Use of the non-selective antagonist α-helical CRF led to attenuation of SEA-induced anorexia, with no effect observed after infusion of the selective CRH-R2 antagonist, astressin-2B (40). This supported the hypothesis that SEA treatment increases

central release of CRH, which acts mainly through CRH-R1 to inhibit food intake. Moreover, given the view that CRH-R1 may suppress food intake under conditions of stressor exposure (69), this data supports the hypothesis for an increased anxiety-like state induced by SEA challenge.

4.2. The Mediating Role of Cytokines

A key property of SAgs is their ability to increase the production of cytokines. Cytokines constitute the soluble mediators of intercellular communication within the immune system, although it is recognized that the cellular origins of cytokines extend beyond the immune system to include endothelial cells, endocrine tissue, and the brain. Within the immune system, cytokine functions include promotion of cellular proliferation, differentiation and implementation of effector functions such as cytotoxicity and antibody production. These effects are consistent with the protective aspects of pathogen-directed immunological responding. Further regulatory functions supported by cytokines, include suppression of cytokine production and cellular function in and of itself, as well as reduction of leukocyte numbers through apoptosis.

The two major cytokines produced in response to an acute injection of SEA or SEB are IL-2 and TNFα, which have both been shown to exert neurobiological effects. The acute effects of IL-2, however, have not been documented in relation to gustatory behavior, but rather dopamine-related changes and behavioral activity in the presence of novelty (70), and disruption of intracranial self-stimulation, a measure of hedonic activity (71). However, TNFα has been shown to produce anorexia and sickness behavior, as well as activation of the HPA axis (72, 73). Consequently, it has proven relevant as a potential mechanism for SEA-induced behavioral changes in the context of gustatory neophobic behavior. Indeed, recently it was shown that SEA challenge increased central *c-fos* induction in limbic brain regions, and this was absent in animals deficient for TNFα production (TNF-knockout mice) (54). Furthermore, it was shown that TNFα knockout mice failed to display anorexic behavior and a corticosterone response to SEA (54). The role of TNFα was further corroborated using immunoneutralization of systemic TNFα, in that antiserum for TNFα blocked the corticosterone response and anorexia in wildtype mice given SEA (ibid). Therefore, it was evident from these results that an important mediational role exists for TNFα in the behavioral, endocrine and neurobiological effects of SEA treatment. Whether the same is true for SEB remains to be determined.

This latter conclusion regarding TNFα was conducted after an acute injection of SEA. More recent work showed persistent corticosterone responses and anorexic behavior after 2-3 SEA injections, which still produced significant TNFα production (43). However, the magnitude of the TNFα response was reduced by close to 40-50% after two and three injections. Moreover, anorexic behavior was no longer evident after three injections, while the corticosterone response persisted after the third injection; this suggested potentially separate immunological mechanisms provoking behavioral and endocrine changes due to SEA challenge (43). Whether TNFα is an important mediator even after repeated exposures to SEA remains to be determined, although there does not appear to be a strong case for IL-1β as an important mediator of SAg effects. That is, IL-1β levels increased substantially after repeated injections of SEA and were, in fact, quite elevated after four injections of SEA, when both endocrine and anorexic effects of SEA were no longer present (43). Moreover, in IL-1 receptor knockout mice, the level of anorexia after SEA and SEB challenge did not differ from wildtype animals (53, 54).

5. PERSPECTIVES

This review has focused on the impact of two bacterial superantigens, SEA and SEB, on two of the major aspects of CNS function assessed in the context of immunological challenge: sickness behavior and neuroendocrine reactivity. Activation of the HPA axis has long been recognized in response to injections of IL-1 and LPS, which are perhaps the most potent stimuli for this component of the neuroendocrine system. However, as stated above, TNFα has also been found to be a strong inducer of sickness behavior and HPA axis responsiveness. In the specific studies involving SEA, it was determined that the observed endocrine and anorexic effects were solely dependent on TNFα (54). This degree of dependence has not been observed for LPS, where multiple cytokines (IL-1, IL-6 and TNF) can contribute to the pituitary-adrenal response (74-76). What is important about these data, when the CNS impact of different bacterial toxins is considered, is the common meditational role of these cytokines, and in particular, TNFα. In the case of bacterial SAgs, however, T cell cytokines are also elaborated, although the literature is not very supportive of IL-2 and IFNγ being strong inducers of sickness behavior and HPA axis activation, at least under acute conditions (56, 77). However, at least for IL-2, there is good evidence for CNS effects, such as anhedonia and dopamine release (77, 78). Consequently, the use of SAgs will continue to be a useful model for studying the induction of endogenous T cell cytokines and their impact on CNS function.

Given the behavioral effects that were noted for SEA and SEB, and the lack of malaise that was induced, it is interesting to speculate whether the results reflect the recruitment of an anxiety-related behavioral inhibition system (79). Indeed, increased amygdaloid activation promotes behavioral inhibition in humans (80), and may be associated with impaired feedback suppression by executive regions such as the prefrontal areas of the frontal lobe (81). Consideration of the areas showing increased

excitatory input following SAg administration (viz., the central nucleus of the amygdala, bed nucleus of the stria terminalis, septum, and prefrontal cortex (38), would suggest this as an important hypothesis to test in future psychoneuroimmunological studies utilizing doses of staphylococcal enterotoxins, as well as endotoxins, that do not produce frank malaise, thereby allowing for the assessment of behavioral alterations that involve higher-order cognitive and emotional systems.

Finally, the potential clinical relevance of these studies and those of toxin administration in general should be considered. In essence, the use of SAgs and any other toxin (eg., LPS), is based on the need to model infection-related circumstances that might shed light on neural-immune interactions. Infection is a dynamic process that has a localized origin (eg., lung, gut, wound) and spreads as a result of pathogen replication, followed by ongoing interactions with innate and adaptive components of the immune apparatus. Therefore, bolus injection models serve only to provide important information about the potential mechanisms and sets of interactions that may be generated by immunological, endocrine and neurobehavioral processes solicited by introduction of the isolated bacterial toxin. Further research is required to examine within the temporal framework of a progressive infection how neural-immune interactions may be similar or different. At the very least, body weight loss and appetite reduction are typical of chronic infections, and in this regard the bolus injection models accurately reflect metabolic and motivational changes that individuals may undergo during infectious illness. Indeed, efforts are underway to develop specific antagonists for superantigenic molecules. The efficacy of these antagonists may potentially reduce many of the severe pathological effects of staphylococcal and streptococcal infections, where T cell activation by superantigenic exotoxins is likely to occur. Moreover, should antagonists only partially reduce the capability of SAgs to stimulate T cells, further antagonism of TNFα, and possibly other cytokines, will serve to reduce the neurobiological effects that ensue from infection, thereby reducing changes in body weight, and other motivational, emotional and cognitive alterations are likely to result from activation of stress systems in the brain.

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