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NEUROIMMUNOMODULATION VIA LIMBIC STRUCTURES — THE NEUROANATOMY OF PSYCHOIMMUNOLOGY

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Abstract—During the last 20 years, mutual communications between the immune, the endocrine and the nervous systems have been defined on the basis of physiological, cellular, and molecular data. Nevertheless, a major problem in the new discipline "Psychoneuroimmunology" is that controversial data and differences in the interpretation of the results make it difficult to obtain a comprehensive overview of the implications of immunoneuroendocrine interactions in the maintenance of physiological homeostasis, as well as in the initiation and the course of pathological conditions within these systems. In this article, we will first discuss the afferent pathways by which immune cells may affect CNS functions and, conversely, how neural tissues can influence the peripheral immune response. We will then review recent data, which emphasize the (patho)physiological roles of hippocampal–amygdala structures and the nucleus accumbens in neuroimmunomodulation. Neuronal activity within the hippocampal formation, the amygdaloid body, and the ventral parts of the basal ganglia has been examined most thoroughly in studies on neuroendocrine, autonomic and cognitive functions, or at the level of emotional and psychomotor behaviors. The interplay of these limbic structures with components of the immune system and vice versa, however, is still less defined. We will attempt to review and discuss this area of research taking into account recent evidences for neuroendocrine immunoregulation via limbic neuronal systems, as well as the influence of cytokines on synaptic transmission, neuronal growth and survival in these brain regions. Finally, the role of limbic structures in stress responses and conditioning of immune reactivity will be commented. Based on these data, we propose new directions of future research.

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ABBREVIATIONS

ACTH	Adrenocorticotropin	CNS	Central nervous system
AP	Area postrema	ConA	Concanavalin A
AVP	Arginine vasopressin	CRH/CRF	Corticotropin-releasing hormone/corticotropin-releasing factor
BBB	Blood–brain barrier		
BDNF	Brain-derived neurotrophic factor	CVO	Circumventricular organ
BLA	Basolateral amygdala	DN cells	Double negative (CD4/CD8) cells (immature T-lymphocytes)
BST	Bed nucleus of the stria terminalis		
CA	Cornu Ammonis (field of hippocampal formation)	DP cells	Double positive (CD4/CD8) cells (immature T-lymphocytes)
CCK	Cholecystokinin	EPSP	Excitatory postsynaptic potential
CeMA	Centromedial amygdala	F344 rat	Fischer 344 rat
CGRP	Calcitonin gene-related peptide	GABA	γ-Aminobutyric acid

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ABBREVIATIONS *(continued)*

GALT	Gut-associated lymphoid tissue
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GR	Glucocorticoid receptor
HF	Hippocampal formation
HIV	Human immunodeficiency virus
HPA axis	Hypothalamic–pituitary–adrenal axis
5-HIAA	5-Hydroxyindole acetic acid
5-HT	5-Hydroxytryptamine (serotonin)
i.c.v.	Intracerebroventricular
IFN	Interferon
IL	Interleukin
IL-1R	Interleukin-1 receptor
IL-1RA	Interleukin-1 receptor antagonist
i.p.	Intraperitoneal
IPSP	Inhibitory postsynaptic potential
i.v.	Intravenous
LPS	Lipopolysaccharide
LTP	Long-term potentiation
ME	Median eminence
MR	Mineralocorticoid receptor
mRNA	Messenger ribonucleic acid
NE	Norepinephrine
NGF	Nerve growth factor
NK cells	Natural killer cells
NMDA	*N*-methyl-D-aspartic acid
NO	Nitric oxide
NZB/NZW	New Zealand (black/white) mice
OB rat	Olfactory bulbectomized rat
OVLT	Organum vasculosum laminae terminalis
PACAP	Pituitary adenylate cyclase activating polypeptide
PAG	Periaqueductal grey
PG	Prostaglandin
PHA	Phytohemagglutinin
PNS	Peripheral nervous system
PTP	Post-tetanic potentiation
SD rat	Sprague Dawley rat
SFO	Subfornical organ
SI	Substantia innominata
SP cells	Single positive (CD4/CD8) cells (mature T-lymphocytes)
ST	Stria terminalis
STP	Short-term potentiation
TGFβ	Transforming growth factor β
TNF	Tumor necrosis factor
VIP	Vasoactive intestinal polypeptide

1. INTRODUCTION

Over the past several years, our knowledge of reciprocal intersystem communications involving the immune, the endocrine, the peripheral (PNS) and central nervous systems (CNS) has exponentially grown. This field of science gains the attention of both basic scientists and clinicians to define new pathophysiological concepts in autoimmune (Schauenstein *et al.*, 1987; Sternberg *et al.*, 1989a, 1989b; Mason *et al.*, 1990; Takasu *et al.*, 1990, 1993; Hu *et al.*, 1993; Jafarian Tehrani *et al.*, 1994), allergic (Undem *et al.*, 1995) and infectious diseases (Blum *et al.*, 1992; Duvaux-Miret *et al.*, 1992), stress conditions (Khansari *et al.*, 1990; Hoffman-Goetz and Pedersen, 1994), as well as affective disorders (Irwin *et al.*, 1991; Evans *et al.*, 1992; Maes *et al.*, 1993), and dementia (Irwin *et al.*, 1991; Vandenabeele and Fiers, 1991). Much of our understanding of neuroimmunomodulation is derived from earlier studies documenting the effects of stress on immune functions (Dantzer and Kelley, 1989). The data are partly controversial, which may be due to species differences, to the fact that different qualities and/or doses of stressors may affect immune reactions in different ways (Rinner *et al.*, 1992), and to individual abilities to cope with one and the same stressor (Ader *et al.*, 1995). Besides immunoregulation by the CNS, it has become increasingly evident that the production of neuroendocrine peptides by immune cells is physiologically relevant to both the immune and the nervous system (summarized by Blalock, 1992; and by Blalock, 1994). However, our knowledge about the ascending immune–brain routes, and the function of brain regions, sometimes referred to as "higher brain centers", in neuroimmunological interactions is still fragmentary. This article, besides describing afferent routes by which immune cells may modify CNS functions and summarizing the most prominent efferent pathways involved in brain–immune communications, presents a brief introduction into the broad range of limbic effector functions, and a detailed description of the specific roles of the hippocampal–amygdala group as well as the ventral striatopallidal system in neuroimmunomodulation (Fig. 1).

2. NEUROIMMUNE COMMUNICATIONS

The concept of a dialog between immune cells and neural tissues is based on three requirements:

1. Nerve terminals directly contact immune cells. The noradrenergic as well as the peptidergic innervation of lymphoid organs is best documented in rodents. Within the spleen at both light and electron microscopic levels, norepinephrine (NE)–nerve terminals have been observed in close apposition to lymphocytes (Felten and Olschowka, 1987). The authors described these contacts as an even more regular and intimate membrane relationship than between nerve terminals and smooth muscle cells, and defined these associations as "synaptic-like" contacts, where transmitter release and postsynaptic receptor activation most likely occur. Noradrenergic postganglionic sympathetic nerve fibers also have been detected in primary lymphoid organs, such as bone marrow and thymus (reviewed by Felten *et al.*, 1987), and neuropeptide-containing nerve fibers have been shown to distribute in lymphatic tissues among lymphocytes and mast cells (Bienenstock *et al.*, 1987; Stead *et al.*, 1987; Bellinger *et al.*, 1990). More recent evidence clearly shows an equivalent anatomical link between the nervous and immune system in the cetacean, *Delphinapterus leucas* (beluga whale). Tyrosine hydroxylase and neuropeptide Y positive nerve profiles were observed not only in systemic lymphoid organs, such as spleen, thymus, tonsil, or assorted lymph nodes, but also in gut-associated lymphoid tissue (GALT) (Romano *et al.*, 1994). As to the role of neurotrophic factors in the induction of sympathetic innervation of immune organs a recent *in vitro* study demonstrated that interleukins, such as IL-1,

IL-3 and IL-6, as well as granulocyte-macrophage colony-stimulating factor (GM-CSF), can induce sympathetic neurite outgrowth, either via nerve growth factor (NGF) production or in an NGF-independent manner (Kannan *et al.*, 1996). Although cholinergic signals markedly affect immune functions (Schauenstein *et al.*, 1994), the cholinergic innervation of immune organs is less described and, in the case of the thymus, is a point of controversy (Bulloch and Moore, 1981; Fatani *et al.*, 1986; Nance *et al.*, 1987; Micic *et al.*, 1994). However, recent data by Niijima (1995) apparently confirmed the vagal innervation of the rat thymus by means of electrophysiological techniques.

2. Both organ systems share common receptors and ligands. In several studies, remarkable concentrations of binding sites for a number of neurotransmitters or -peptides have been identified on the surface of white blood cells (Gordon *et al.*, 1978; Ovadia and Abramsky, 1987; Hellstrand and Hermodsson, 1990a, 1990b; Lignon *et al.*, 1991; Carr, 1992; Landmann, 1992; Kaneda *et al.*, 1993; Costa *et al.*, 1994). Furthermore, immune cells are found to be equipped to produce not only cytokines, but also neurohormones, neuropeptides (Akira *et al.*, 1990; Blalock, 1992, 1994) and neurotransmitters, such as catecholamines (Bergquist *et al.*, 1994) and, as reported by our group, acetylcholine (Rinner and Schauenstein, 1993). On the other hand, interleukin (IL)-1β as well as mRNA homologous to IL-1 receptor (IL-1R) type I are expressed in cultured sympathetic ganglia (Freidin *et al.*, 1992; Hart *et al.*, 1993) and 1L-1β binding sites have been demonstrated on paraganglia in the rat liver hilus and hepatic vagus (Goehler *et al.*, 1994). IL-6 and IL-6R transcripts were found in postnatal rat sympathetic and sensory ganglia (Gadient and Otten, 1996). IL-6R mRNA has been detected in cultured primary rat sympathetic neurons as well as in the pheochromocytoma cell line PC12, and this expression can be modulated by tumor necrosis factor (TNF)-α (März *et al.*, 1996). Research on nematode infections in small mammals revealed an enhanced expression of IL-1α, IL-1β, IL-6 and TNF-α mRNA and protein in the longitudinal muscle myenteric plexus of the inflamed intestine of rats (Khan and Collins, 1994). Additionally, a continuously growing number of reports shows that cytokines and their receptors are

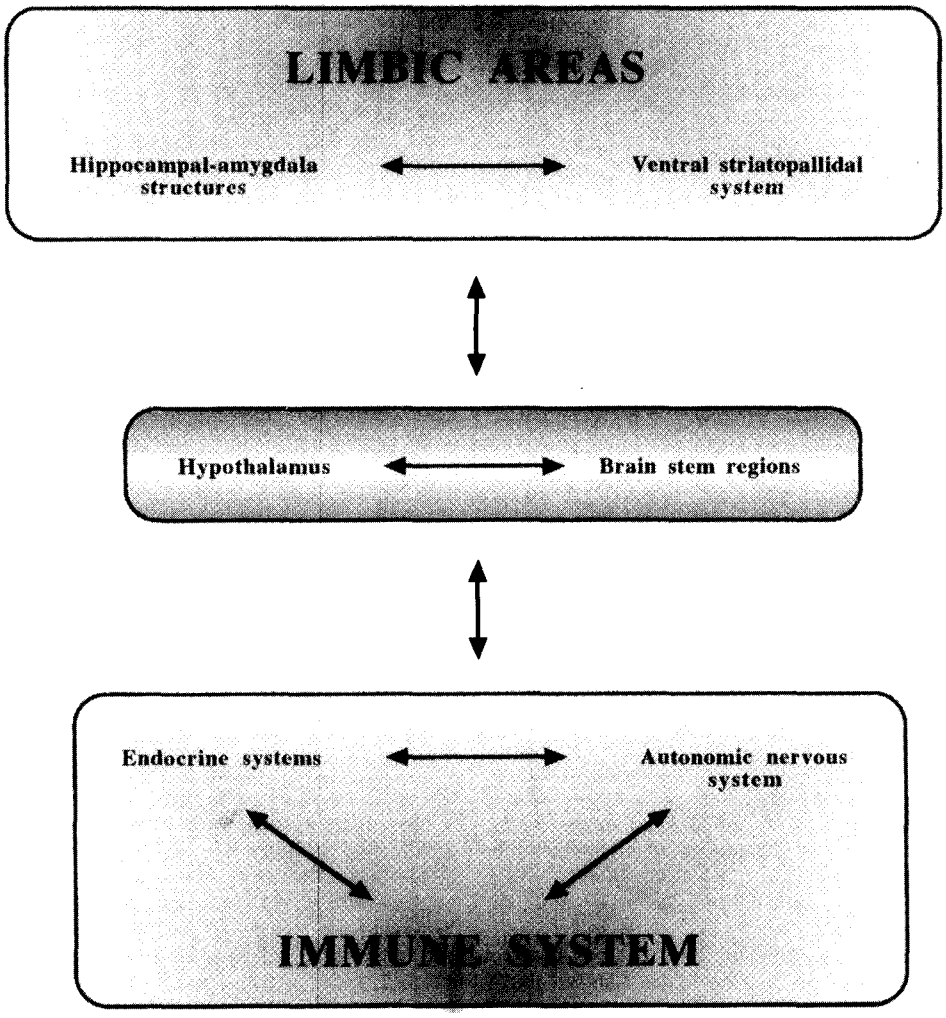

Fig. 1. Limbic areas in neuroimmunomodulation.

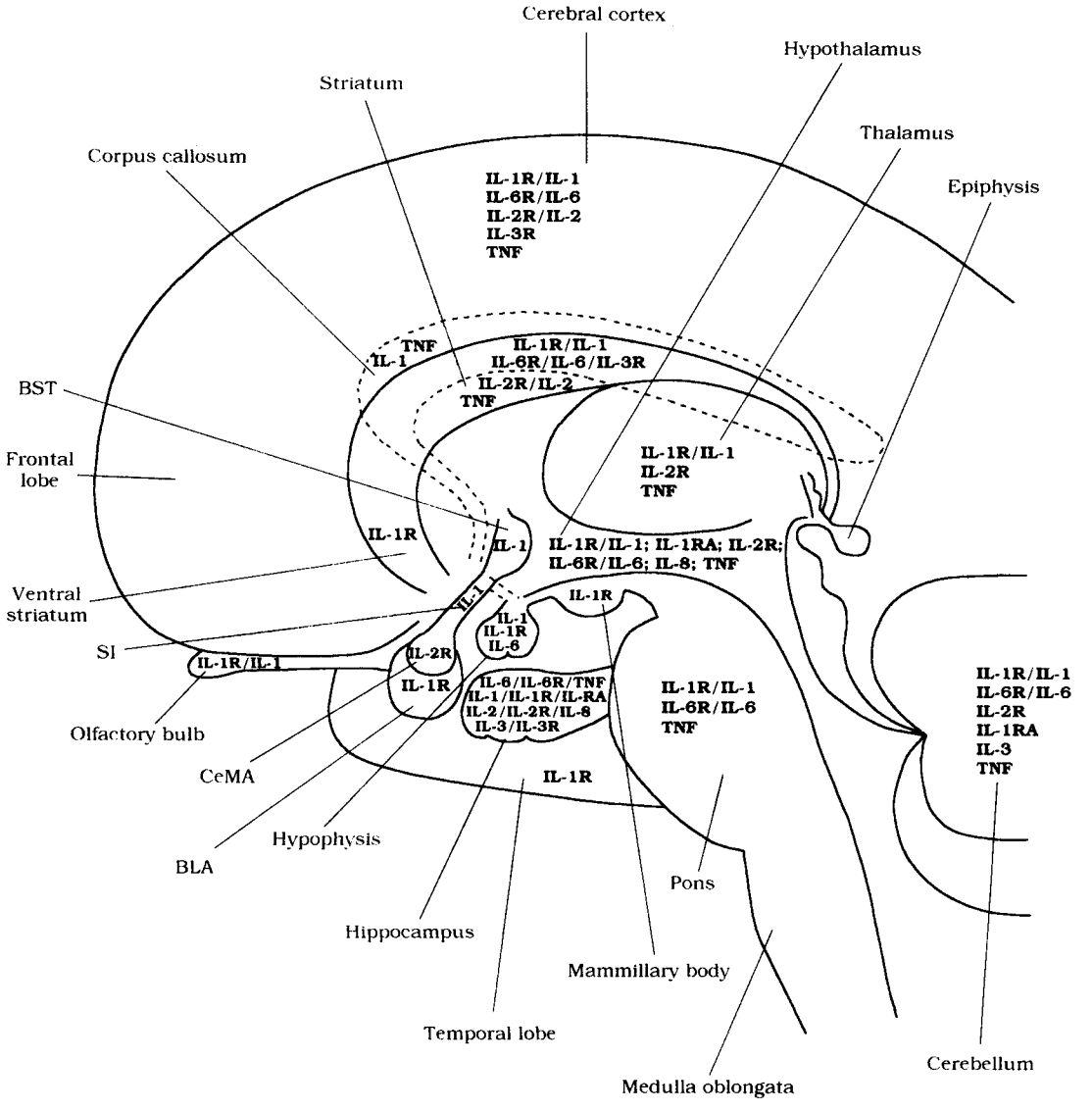

Fig. 2. Schematic presentation of cytokines and their receptors in the brain as described in animal models (mouse/rat/pig) and humans. Abbreviations: CeMA, centromedial amygdala; BLA, basolateral amygdala; BST, bed nucleus of the stria terminalis; SI, substantia innominata.

ubiquitously distributed in the brain (Fig. 2) and, apart from infiltrating leukocytes, glial cells, brain endothelial cells, as well as neurons have been described as major cellular sources (Frei *et al.*, 1985; Farrar *et al.*, 1987; Araujo *et al.*, 1989; Lapchak *et al.*, 1991; Licinio *et al.*, 1991, 1992; Gadient and Otten, 1994; Petitto and Huang, 1994; Schöbitz *et al.*, 1994a, review; Van Dam *et al.*, 1996). However, as clearly demonstrated in a recent study, which examined the effects of IL-1β on food intake, body temperature and pain sensitivity in hypothalamus and thalamus, cytokines have very selective neuroanatomical sites of action (Sellami and de Beaurepaire, 1995).

3. Mutual ligand–receptor interactions lead to significant changes in cellular functions in both systems. The evidence for pronounced effects of neurotransmitters and -peptides on immune effector functions has been described extensively (Ader *et al.*, 1991; Goetzl and Sreedharan, 1992). Nevertheless, these results are partly conflicting, which may be explained by the complexity of the systems concerned, and by the use of different experimental approaches. Conversely, cytokines have effects on neural tissues. An i.v. injection of recombinant human IL-1β or human IL-1β fraction has been shown to result in an increase in the efferent activity of the vagal branch to the thymus (Niijima *et al.*, 1995). The activity of adrenal, splenic and renal sympathetic nerves is affected differentially by i.v. administration of human recombinant IL-1β. Whereas adrenal and splenic neural activity increased for more than 2–6 hr, the activity of renal nerves showed only a transient increase followed by a long-lasting suppression (Niijima *et al.*, 1991). Evidences were obtained that IL-1β affects enteric

cholinergic neuronal function (longitudinal muscle myenteric plexus preparations from the rat jejunum/whole preparations of guinea pig ileum, including mucosa) in a dual way, either suppressing or stimulating the electrically evoked release of acetylcholine (Main *et al.*, 1993; Mameya *et al.*, 1995). A similar duality was observed concerning the effects of IL-6 on the evoked release of NE from the rat jejunal myenteric plexus (Rühl *et al.*, 1994). Furthermore, IL-1β has been shown to mediate increases in substance P receptor mRNA in explanted neonatal sympathetic ganglia (Ludlam *et al.*, 1995), IL-1β induces substance P in cultured superior cervical ganglia (Jonakait and Schotland, 1990; Jonakait *et al.*, 1990; Hart *et al.*, 1991), and IL-1α, as well as TNF-α, differentially modulate both substance P and vasoactive intestinal polypeptide (VIP) biosynthesis in adrenomedullary chromaffin cells (Eskay *et al.*, 1992). In addition, cytokines are known to mediate a wide variety of other effects, such as neuroendocrine responses, neuronal growth, autonomic functions, and behavioral activity (reviewed by Schöbitz *et al.*, 1994a).

2.1. Afferent Pathways

Although there is compelling evidence that the peripheral immune system modifies central neural cell functions, the afferent pathways by which immune cells affect the CNS are still far from clear. In the following, two principal mechanisms will be discussed (Fig. 3).

As one mechanism, a humoral route may be involved in neuroimmune communications. Some studies suggested an active transport of cytokines across the blood–brain barrier (BBB) (Gutierrez *et al.*, 1993, 1994; Maness *et al.*, 1995), others supposed an interaction at the level of endothelial cells, which subsequently results in the induction of central prostaglandins (Gottschall *et al.*, 1992a; Van Dam *et al.*, 1993, 1996). Recently it has been found that IL-1β, IL-6 and TNF-α induce changes in the electrical resistance across rat cerebral endothelial cells *in vitro*, and that cytooxygenase activation within endothelial cells is likely to play a key role in this process (De Vries *et al.*, 1996). Alternatively, it has been proposed that soluble signal mediators, such as immune cytokines, may gain entry to the brain through the circumventricular organs (CVOs), which lack a BBB and provide for the exchange of blood-borne high molecular polypeptides between blood and brain (Stitt, 1990; Blatteis, 1992). The CVOs most frequently examined in neuroimmunology are the median eminence (ME) and the organum vasculosum laminae terminalis (OVLT). It has been suggested that the systemic influence of cytokines on hypothalamic–pituitary–adrenal axis (HPA) activity is exerted primarily at the level of nerve terminals in the ME (Matta *et al.*, 1990; Rivest *et al.*, 1992), and the OVLT has been implicated in the pathogenesis of fever (Stitt, 1990; Blatteis, 1992). Recently, Hare *et al.* (1995) showed that CVOs other than the ME and the OVLT are implicated in the immune–brain dialog. Following i.v. treatment with lipopolysaccharide (LPS), an increased number of cells positively staining for Fos could be observed also in the area postrema (AP) and subfornical organ (SFO). Since the neurons in the CVOs are connected with nearby hypothalamic regions and neighboring brain stem regions, Fos protein expression also was investigated in further parts of the brain. LPS-induced increases in the number of Fos-stained cells could be detected in the major noradrenergic cell groups (A1, A2, A6), in the paraventricular and supraoptic nuclei and in limbic structures, such as the bed nucleus of the stria terminalis (BST), the central nucleus of the amygdaloid body, and the ventral septal area. These observations are similar to those reported by others (Gaykema *et al.*, 1995). As reviewed by Johnson and Gross (1993), it is well established that the CVOs contain a number of hormones, neurotransmitters and transmitter-like factors, e.g. adrenocorticotropin (ACTH), angiotensin, enkephalins, neuropeptide Y, VIP, somatostatin, substance P, epinephrine, NE, acetylcholine, serotonin (5-HT), dopamine, γ-aminobutyric acid (GABA), glutamate and aspartate, as well as high concentrations of respective binding sites. Many of these substances with receptors in the CVOs have been shown to be effective in inducing changes in neuronal firing. Together, these neuronal systems can reach many further parts of the CNS, including limbic forebrain structures. Based on these findings, it is reasonable to assume that CVOs have a crucial role in translating cytokine signals into neuronal activity. Considering the concept of a humoral immune–brain route, however, it should be kept in mind that central illness responses, such as fever, also can be observed without detectable elevations of cytokine blood levels (Kluger, 1991).

A second mechanism, by which immune cells modify CNS functions, may involve the PNS. Such a neural immune–brain route would not require changes in systemic cytokine concentrations. Accordingly, the translation of humoral into nerve signals may occur in the periphery, from where the CNS is activated via the most common afferents of the body, i.e. the vagus nerve and/or the nociceptive afferents, which travel in the sympathetic parts of the PNS.

Evidence continues to accumulate in the literature suggesting a prominent role for the vagus in neuroimmunomodulation. Niijima (1992) reported an increased afferent discharge rate of the hepatic branch of the vagus nerve following administration of IL-1β into the portal venous blood. Subdiaphragmatic vagotomy blocked hyperalgesia, produced by i.p. LPS (Watkins *et al.*, 1994a), i.p. IL-1β (Watkins *et al.*, 1994b), and by i.p. TNF-α (Watkins *et al.*, 1995a). More specifically, the i.p. LPS-induced prolonged enhancement of pain responsiveness also is abolished by cutting only the hepatic branch of the vagus (Watkins *et al.*, 1994a), and hepatic macrophages (Kupffer cells) serving as sources for cytokines have been shown to be involved critically in this pathway (Watkins *et al.*, 1994b). Concerning the neurocircuitry of LPS- or cytokine-induced hyperalgesia, data of Watkins *et al.*, 1994a) suggest that afferent information travels via the hepatic vagus to the nucleus tractus solitarius. From here, an efferent pathway arises from the nucleus raphe magnus to the spinal cord via the dorsolateral funiculus involving a spinal substance P, cholecystokinin (CCK), *N*-methyl-D-aspartic acid (NMDA)-nitric oxide (NO)

cascade as well as non-NMDA excitatory amino acid receptors (Watkins *et al.*, 1994c; Wiertelak *et al.*, 1994).

In further support of vagal afferents, subdiaphragmatic vagotomy strongly inhibited endotoxin-induced Fos expression in the paraventricular nucleus of the hypothalamus, specifically in corticotropin-releasing hormone (CRH)-containing cells, and blocked the ACTH response following low-dose i.p. endotoxin treatment (Gaykema *et al.*, 1995). However, hepatic branch vagotomy did not affect endotoxin-induced Fos expression and, rather,

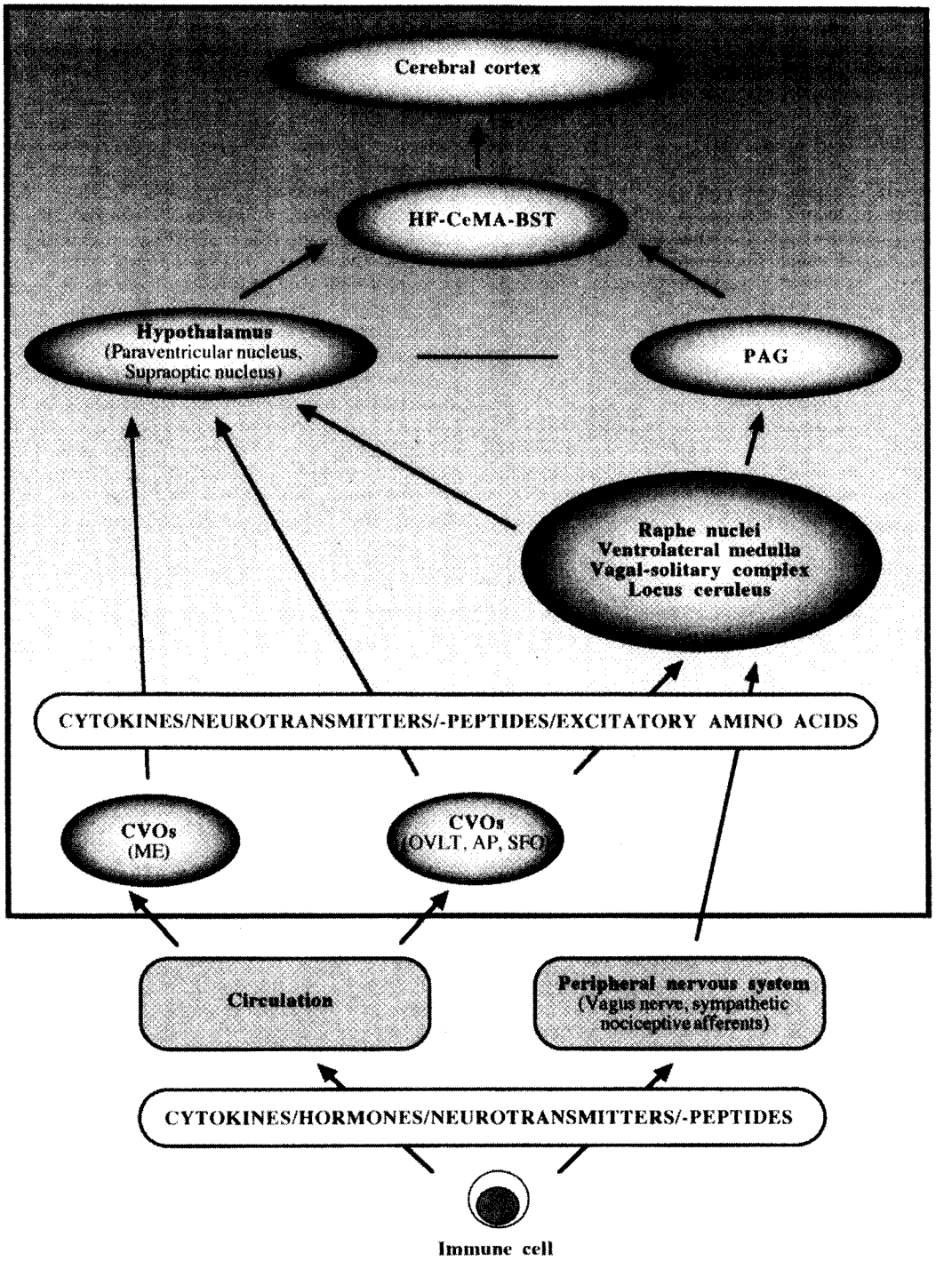

Fig. 3. Afferent pathways in the immune-brain dialog. Abbreviations: CeMA, centromedial amygdala; BST, bed nucleus of the stria terminates; HF, hippocampal formation; PAG, periaqueductal grey; CVOs, circumventricular organs; ME, median eminence; OVLT, organum vasculosum laminae terminalis; AP, area postrema; SFO, subfornical organ.

potentiated the ACTH response to low-dose endotoxin. Thus, different organ-specific impulses from visceral receptors may reach the CNS through different vagal afferents. This notion is supported by findings demonstrating that the activation of vagal afferents mediates a broad range of responses, such as an IL-1β-induced corticosterone elevation and hypothalamic NE depletion (Fleshner *et al.*, 1995), LPS-induced sickness behavior (Bluthé *et al.*, 1994), LPS-induced central IL-1β mRNA expression (Layé *et al.*, 1995), IL-1-induced hyperthermia (Watkins *et al.*, 1995b), LPS-induced fever (Sehic and Blatteis, 1996) and cytokine-induced conditioned taste aversion (Goehler *et al.*, 1995). Apparently in contrast to Fleshner *et al.* (1995), who demonstrated a vagally mediated IL-1β-induced corticosterone increase, our own results in rats revealed that peripheral cholinergic stimulation with physostigmine on days 1 and 2 before immunization with sheep red blood cells (SRBC) strongly suppressed the rise of plasma corticosterone via muscarinergic mechanisms (Rinner and Schauenstein, 1991).

As most of the peripheral pain fibers ascend with the sympathetic innervation, cytokine-induced hyperalgesia also may follow a sympathetic course. In this context, plantar injection of IL-1β was found to enhance neural discharge in dorsal root filaments in response to mechanical and thermal stimulation, and to decrease the threshold for the response to pressure stimulation (Fukuoka *et al.*, 1994). Since substance P mediates peripheral hyperalgesia (Nakamura-Craig and Smith, 1989), and IL-1β regulates the expression of the peptide and its receptor in sympathetic ganglia (see above), cytokines most likely contribute to pain facilitation. On the other hand, interleukins also can induce local analgesic effects. IL-1β and CRF have been found to inhibit pain by releasing opioid peptides from immune cells within inflamed tissue (Stein *et al.*, 1990; Schäfer *et al.*, 1994). Studies on joint inflammation have shown that primary afferents became rapidly sensitized during a developing arthritis (Levine *et al.*, 1986a; Schaible and Schmidt, 1988), and that several neuropeptides, such as substance P, calcitonin gene-related peptide (CGRP), neuropeptide Y, and neurokinin A, appear to be involved in the inflammatory process (Levine *et al.*, 1984; Donaldson *et al.*, 1992; Mapp *et al.*, 1993; Bileviciute *et al.*, 1993, 1995). In addition to these peripheral neurogenic mechanisms, recent data demonstrate that also central, even though different, regulatory mechanisms are involved in the course of adjuvant-induced knee joint monoarthritis. Bileviciute *et al.* (1995) observed various changes in the concentrations of the same neuropeptides in hypothalamus, hippocampus, striatum, and cortex of arthritic rats, but only few correlations between neuropeptide concentrations in brain and periphery. Finally, recent *in vitro* data suggest peptidergic (neurokinin A, VIP) sensory nerve terminals also to be involved in the modulation of antibody responses in the spleen (Hikawa and Takenaka, 1996). However, in spite of the PNS's apparent importance in the immune–brain dialog, it is largely unknown which of the afferent routes and which of the many neurotransmitters are responsible for information processing of a particular type of immune challenge.

2.2. Efferent Pathways

Early studies exclusively examined neuroimmune interactions at the level of the hypothalamus. Besedovsky *et al.* (1975) were the first to describe the neuroendocrine feedback regulation of immune responses via glucocorticoid hormones. This glucocorticoid peak at the time of maximal antibody production after antigenic challenge is caused by central activation of the HPA axis. It contributes to the specificity of immune reactions (Besedovsky *et al.*, 1979), and defects of this circuit predispose to unwanted immune reactions, as suggested by data in animal models with spontaneous (Schauenstein *et al.*, 1987), as well as experimentally induced autoimmune diseases (Sternberg *et al.*, 1989a, 1989b; Mason *et al.*, 1990; Hu *et al.*, 1993). The primary event in this pathway appears to be an increased hypothalamic turnover of NE following immune activation (Besedovsky *et al.*, 1983; Zalcman *et al.*, 1991; Shanks *et al.*, 1994), which can give rise to an activation of CRH neurons (Berkenbosch *et al.*, 1987; Sapolsky *et al.*, 1987). Based on these data, it has long been established that the immune system is modulated by hypothalamic–pituitary (HP) axes (Besedovsky *et al.*, 1986; Rivier and Vale, 1989; Chrousos, 1995; Savino and Dardenne, 1995), and the role of central cytokines in the activation of HP axes has been the subject of numerous studies (Harbuz *et al.*, 1992; reviewed by Schöbitz *et al.*, 1994a).

Besides these neuroendocrine pathways, there is evidence for neural routes, by which the brain regulates peripheral immune functions. Several data suggest the sympathetic nervous system to convey information from the CNS to the peripheral immune system (Sundar *et al.*, 1989, 1990; Croiset *et al.*, 1990; Irwin *et al.*, 1990, 1991, 1992; Irwin, 1994), and adrenoceptor-mediated effects on lymphocyte functions have been defined by several groups, including ourselves (Livnat *et al.*, 1987; Felsner *et al.*, 1992, 1995; Sanders, 1995). The specific role of the sympathetic nervous system in the modulation of peripheral immune activity has been underscored by a number of recent findings showing that (i) sympathetic denervation results in a wide variety of strain-, organ-, or even compartment-specific effects, such as increases in cellular proliferation and lymphocyte migration (Madden *et al.*, 1994a), enhanced macrophage phagocytic function (Lyte *et al.*, 1991), reductions in thymus weight and thymocyte numbers (Tsao *et al.*, 1996), thymocyte apoptosis (Tsao *et al.*, 1996), and heterogeneous alterations in B- or T-cell responsiveness, as well as cytokine (IL-2/IFN-γ) production (Lyte *et al.*, 1991; Madden *et al.*, 1994b); (ii) the IL-2-induced enhancement of an IgM plaque-forming cell response requires an intact sympathetic innervation of the spleen and is blocked selectively by the β-adrenergic antagonist propranolol (Zalcman *et al.*, 1994a); (iii) the immunosuppressive effects of stress on humoral and cell-mediated immune responses of rat splenocytes are mediated via adrenergic fibers of the splenic nerve (Wan *et al.*, 1993); and (iv) local NE release is involved in the regulation of IL-6 secretion in the spleen (Straub *et al.*, 1995). Furthermore, there exists

a large body of evidence suggesting a regulatory role for the sympathetic nervous system in the pathogenesis or progression of diseases, such as experimental and clinical arthritis (Levine *et al.*, 1986a, 1986b, 1988; Felten *et al.*, 1992; Lorton *et al.*, 1996), experimental allergic encephatomyelitis (Chelmicka-Schorr *et al.*, 1988, 1989) and experimental autoimmune myasthenia gravis (Agius *et al.*, 1987).

Regarding immunomodulatory effects of vagal efferent fibers, there is increasing evidence that parasympathetic activity plays a prominent role in thymic lymphopoiesis (Singh and Fatani, 1988), apoptosis, as demonstrated by our group (Rinner *et al.*, 1994), and lymphocyte traffic from thymus to peripheral lymphoid organs. Antonica *et al.* (1996) observed an increased export of immature $CD4^+CD8^+$, double positive (DP), and $CD4^-CD8^-$, double negative (DN), cells from mouse thymus following monolateral vagal denervation, and that both DP and DN cells migrate more consistently to lymph nodes and spleen of vagotomized mice compared to controls. In parallel, the percentage of single positive (SP) cells was decreased in peripheral organs. These results, together with the findings of a preeminent role of the thymic microenvironment in positive and negative selection of developing T-cells, and thereby in the avoidance of autoimmunity (Boyd *et al.*, 1993), emphasize the complex interactions between the nervous and immune systems.

As a further efferent mechanism, central LPS as such, or a fragment, could leak through the BBB and induce cytokine production in the periphery. This has been suggested by comparing the time-course of serum IL-6 induction after peripheral or central LPS administration (De Simoni *et al.*, 1992, 1995; Gottschall *et al.*, 1992b). Further descending brain–immune routes were identified by showing that, aside from CRH (Schulte *et al.*, 1994), several other neuropeptides, such as substance P and VIP (Stanisz *et al.*, 1986; Laurenzi *et al.*, 1990; Spangelo *et al.*, 1990; Agro and Stanisz, 1995), can transmit central effects towards the periphery, and there is growing evidence that central opioid pathways are critically involved (De Simoni *et al.*, 1993; Fecho *et al.*, 1996). However, despite intense research efforts, many aspects of the CNS-mediated immunoregulation are still poorly understood. Nor do we exactly know in which way, or to what extent, different brain sites influence specific immune activities. For example, Hernandez *et al.* (1993) reported that injection of morphine into either the third ventricle or the anterior hypothalamus significantly suppressed blood lymphocyte proliferation. Weber and Pert (1989) examined the functional role of the midbrain periaqueductal grey (PAG) in opiate-induced immunosuppression. Microinjection of morphine into the PAG resulted in a rapid suppression of splenic natural killer (NK) cell activity. Injection into the anterior hypothalamus, arcuate nucleus, medial amygdala, medial thalamus, and dorsal hippocampus was without an effect on NK activity. Recently, the neuronal networks connecting the PAG with a large number of brain structures, including the nucleus raphe magnus, ventrolateral medulla, hypothalamus, amygdala, and prefrontal cortex, have been described in detail by Behbehani (1995). In addition, this author reviewed the pharmacology of PAG-mediated pain, analgesia, anxiety and fear, vocalization or autonomic regulation, which mainly involves opiates, GABAergic interneurons, neurotensin, substance P, excitatory amino acids, catecholamines, 5-HT-containing cell bodies and CCK-responsive neurons. None the less, little or virtually nothing is known whether, how, or to what extent all these neurotransmitters are implicated in brain immunomodulation via specific structures such as the PAG.

The issue of neuroimmunomodulation is complicated further by the fact that, aside from hypothalamus and brain stem regions, additional brain strictures are involved in the modulation of peripheral immune responses. Selective alterations of different components of the immune system have been observed in animals subjected to experimental lesions of the cerebral cortex (Renoux *et al.*, 1987), the lateral septal area (Wetmore *et al.*, 1994), the nucleus basalis magnocellularis, the equivalent of Meynert's nucleus in the primate (Cherkaoui *et al.*, 1990), and further limbic structures (see below). In view of the close relations between cholinergic activity and immunity (see above), it should be kept in mind that the basal nucleus of Meynert contains, similar to the septum, not only large cholinergic but also GABAergic neurons, and has been shown to be involved in learning, memory and attention (Lamour *et al.*, 1989; Durkin, 1994; Muir *et al.*, 1994). In addition, septum and nucleus basalis of Meynert serve as one of the diverse neuroanatomical substrates providing for cortical activation or arousal (Riekkinen *et al.*, 1991; Osborne, 1994). However, at present the specific role of both these structures in neuroimmunology has not been defined, and should be subject of future investigations.

What we can conclude from this diversity of information is that (i) the brain as a whole participates in the modulation of peripheral immunity; (ii) humoral and neural pathways convey information from the brain to the peripheral immune system; (iii) neuroimmunomodulation includes brain sites involved in emotional processing and cognitive functions as the neuroanatomical substrate of psychoimmunomodulation.

3. THE LIMBIC SYSTEM

The "limbic system" is used as a collective term for various brain structures in the basomedial telencephalon, diencephalon and mesencephalon, all of which have been implicated in cognitive functions, emotions, behavior, neuroendocrine and autonomic responses. The most commonly cited structures comprise the hippocampal formation with the hippocampus, dentate gyrus and subiculum, as well as the amygdaloid body, in particular a recently reconsidered brain region referred to as the "extended amygdala" (centromedial amygdaloid–bed nucleus of the stria terminals continuum) (Martin *et al.*, 1991; Schmued, 1994; Heimer, 1995a). Aside from these areas, many other parts of the brain, including the old portions of the "rhinencephalon",

the cingulate gyrus, parahippocampal gyrus with the entorhinal cortex and praesubiculum, the ventral parts of the striatal complex, septum, anterior thalamic nuclei, medial thalamic nuclei and the habenula, have been recognized to be "limbic" (Heimer, 1995b). It is generally accepted that all these structures are related to each other as well as to neighboring non-limbic areas by a network of widespread fiber projections providing the basis of highly organized neuronal circuits. However, it is all the same now fairly certain that there does not exist an anatomical or functional unit referable to a "limbic system". Therefore, for clarity's sake, the following chapters will focus on the roles of the hippocampal–amygdala group and the nucleus accumbens in psychoneuroimmunomodulation. As one pathway, the hippocampal formation is related reciprocally with the amygdaloid body via the amygdalohippocampal fibers (Aggleton, 1986; Amaral, 1986; Mello *et al.*, 1992). The extended amygdala itself projects to many regions in the hypothalamus as well as to somatomotor and autonomic areas in the brain stem, with further effects on the spinal cord (Martin *et al.*, 1991; Schmued, 1994; Heimer, 1995a). On the other hand, as shown e.g. in the visual system, information processing also may involve the simultaneous activation of different areas or distributed neuronal networks, including cortico-cortical re-entrant circuits (Bullier and Nowak, 1995). Besides the visual cortex, other re-entrant loops have been recognized, which appear to involve the basal ganglia (Alexander *et al.*, 1989; Parent and Hazrati, 1995). Accordingly, as a second route, a mesolimbic component of such a cortico-basal ganglia–thalamocortical re-entrant circuit is considered. The nucleus accumbens is part of the "ventral striatopallidal system" (Heimer, 1995c), which primarily receives inputs from the hippocampal formation, the basolateral amygdala, and temporal, as well as prefrontal cortical areas. Interestingly, some impulses return to the anterior cingulate area via the mediodorsal thalamic nucleus (Heimer, 1995d). The nucleus accumbens itself is known to be of relevance to both cognitive functions (Schacter *et al.*, 1989; Salamone, 1994), as well as the central processing of immune signals (see below). Thus, psychoimmunomodulation appears to be more complex than previously supposed. Figure 4 is an attempt to visualize both routes in one scheme.

In the following, some functional characteristics of limbic structures will be summarized briefly. The hippocampal formation has been attributed with important functions in learning processes (Grossberg and Merrill, 1992), memory and retrieval (Squire and Zola-Morgan, 1989; Mishkin, 1993) and, accordingly, has been implicated in Alzheimer's disease (Hyman *et al.*, 1984; Mullan, 1993; Wakabayashi *et al.*, 1994). The amygdala is critically involved in the processing of emotional stimuli (Davis, 1992), whereby hemispheric differences have been observed (Adamec and Morgan, 1994), and recent evidence suggests that amygdala neurons serve important functions in emotional learning and memory storage (reviewed by Ono *et al.*, 1995). Local infusion of CRF into the amygdala has been found to affect aggressive as well as investigative behavior in rats (Liang and Lee, 1988; Elkabir *et al.*, 1990). Furthermore, the medial amygdala is well established to modulate defensive rage behavior (Shaikh *et al.*, 1993), as well as predatory attack behavior in the cat (Han *et al.*, 1996a, 1996b). On the one hand, medial amygdaloid stimulation has been shown to facilitate defensive rage behavior elicited from the medial hypothalamus involving a substance P pathway from the medial amygdala to the medial hypothalamus (Shaikh *et al.*, 1993). On the other hand, the medial amygdala suppresses predatory attack behavior elicited from the lateral hypothalamus via a disynaptic pathway which, first, runs from the medial amygdala to the ventromedial hypothalamus utilizing substance P as excitatory neurotransmitter and, second, includes inhibitory GABAergic projections from the ventromedial hypothalamus to the lateral hypothalamus (Han *et al.*, 1996a, 1996b). These data indicate close relationships between limbic areas and different parts of the hypothalamus, supporting the notion of multifunctional neuronal networks involved in the control of behavioral activity. In view of the importance of such distributed organization, it would be of special interest to determine whether similar pathways exist in mediating immune-induced behavioral responses. In addition, hippocampus and amygdala both have been shown to contain receptors for corticotropin-releasing factor (CRF) (Millan *et al.*, 1986; Lovenberg *et al.*, 1995; Avishai-Eliner *et al.*, 1996), glucocorticoids (GR) (Sapolsky *et al.*, 1983; McEwen *et al.*, 1986; De Kloet *et al.*, 1994) and mineralocorticoids (MR) (Coirini *et al.*, 1985; McEwen *et al.*, 1986; De Kloet *et al.*, 1994). It has become clear that the basal and stress-induced HPA activity is coordinately controlled by the high-affinity MRs (Type I receptors) and the low-affinity GRs (Type II receptors) (De Kloet, 1991), and that the hippocampus, particularly the dorsal part, plays a prominent role in modulating the negative feedback effects of glucocorticoids on HPA axis activity (review by Jacobson and Sapolsky, 1991; Feldman and Weidenfeld, 1993). In a series of papers (Beaulieu *et al.*, 1986, 1987; Feldman *et al.*, 1994), the central and medial nucleus of the amygdala were identified as a regulatory sites of ACTH secretion. Back in the seventies, Carroll *et al.* (1976) already argued that a limbic–hypothalamus disinhibition of the pituitary–adrenal axis occurs in patients with depressive disorders. Aside from adrenal steroids, gonadal and thyroid hormones also have been shown to influence hippocampal physiology and morphology (Gould *et al.*, 1991; McEwen and Woolley, 1994; Woolley and McEwen, 1994). However, by far the majority of studies on limbic structures have addressed their roles in the neuroendocrine stress response, and several methods including psychosocial stress, immobilization and cold restraint-induced gastric ulcerogenesis have been used in animal models to examine the effects of stressful stimulation on hippocampus, amygdala, BST, as well as nucleus accumbens (see below). Given these diverse functions of limbic neuronal systems, it is not surprising that a large number of receptor proteins, neuropeptides

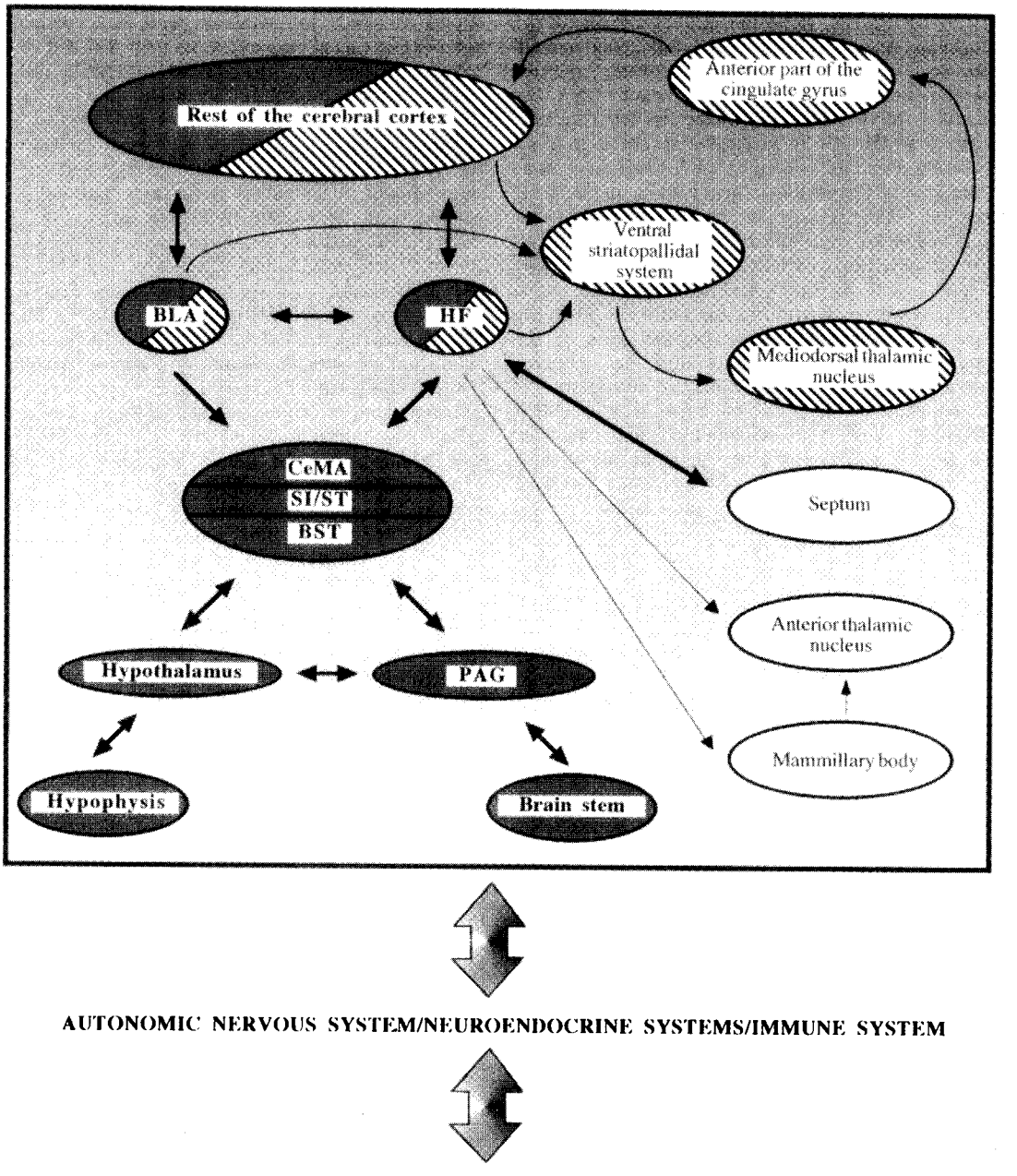

Fig. 4. Processing of external stimuli by hippocampal–amygdala and/or ventral striatopallidal structures. Pathway 1 (solid): cortex–"extended amygdala"–(centromedial amygdaloid–bed nucleus of the stria terminalis continuum). Pathway 2 (striped): cortico-basal ganglia–thalamo-cortical "re-entrant loop" via the "ventral striatopallidal system". Additional connections (plain). Abbreviations: CeMA, centromedial amygdala; BLA, basolateral amygdala; BST, bed nucleus of the stria terminalis; HF, hippocampal formation; SI, substantia innominata; ST, stria terminalis; PAG, periaqueductal grey.

and neurotransmitters have been identified in these regions. Current data suggest the involvement of noradrenergic (Beaulieu *et al.*, 1987; Dalmaz *et al.*, 1993; Gobert *et al.*, 1993; Kiss *et al.*, 1995), cholinergic (Finkelstein *et al.*, 1985; Gilad *et al.*, 1985; Dalmaz *et al.*, 1993; Costa *et al.*, 1994; Aigner, 1995; Rieck *et al.*, 1995; Komourian and Quik, 1996; Tice *et al.*, 1996), GABAergic (Rainnie *et al.*, 1991a, 1991b; Mello *et al.*, 1992; Orchinik *et al.*, 1995), serotonergic (Beaulieu *et al.*, 1986; Martin *et al.*, 1992; Holmes *et al.*, 1995; Matsumoto *et al.*, 1995; Zhong and Ciaranello, 1995; Morales *et al.*, 1996), dopaminergic (Beaulieu *et al.*, 1987; Gasbarri *et al.*, 1994; Nistico *et al.*, 1994) and glutamatergic mechanisms (Clark and Cotman, 1992; Liang *et al.*, 1994; Aigner, 1995; Blümcke *et al.*, 1995; Day *et al.*,

1995; Arai and Lynch, 1996), as well as several neuropeptides, including CRF (Ray *et al.*, 1993; Kalin *et al.*, 1994), arginine vasopressin (AVP) (De Vries *et al.*, 1985; Brinton *et al.*, 1994; Hirasawa *et al.*, 1994; Van Wimersma Greidanus and Maigret, 1996), oxytocin (Van Wimersma Greidanus and Maigret, 1996), substance P (Rieck *et al.*, 1995; Han *et al.*, 1996a), VIP (Léránth and Frotscher, 1983; Roberts *et al.*, 1984), pituitary adenylate cyclase activating polypeptide (PACAP) (Palkovits *et al.*, 1995), neurotensin (Roberts *et al.*, 1984), CCK (Roberts *et al.*, 1984; Hamilton and Freeman, 1995), neuropeptide Y (Zachrisson *et al.*, 1995), enkephalins (Rieck *et al.*, 1995), dynorphin (Watanabe *et al.*, 1995a), and somatostatin (Roberts *et al.*, 1984; Obata-Tsuto, 1987; Zachrisson *et al.*, 1995).

Besides these classical neuronal and neuroendocrine components, the expression of cytokines and their receptors has been demonstrated in all limbic areas, as outlined in Table 1. Noteworthy in this regard is that spontaneous autoimmune diseases in the NZB and (NZB/NZW)F1 mouse model have been shown to be associated with a deficit in the density of IL-1R in the dentate gyrus exclusively (Jafarian Tehrani *et al.*, 1994). The IL-1β expression in the hippocampal formation also is affected by chronic exposure to morphine. Using immunocytochemical analysis, Patel *et al.* (1996) recently reported a marked decrease of IL-1β staining in the polymorphic region of the dentate gyrus and CA1–CA3 subfields of the rat hippocampus after chronic treatment with morphine. Finally, classical neurotransmitters such as 5-HT even at very low concentrations were recently shown to induce cytokine mRNA expression in rat primary hippocampal astrocytes (Pousset *et al.*, 1996).

Table 1. Cytokines and their Receptors in Limbic Areas

Receptor	Limbic area
IL-1R	Molecular and pyramidal cell layer of the hippocampus
	Molecular and granule cell layer of the dentate gyrus
	Cingulate cortex
	Entorhinal cortex
	Subiculum
	Basolateral amygdala
	Olfactory bulb
	Medial habenula
	Anterior dorsal thalamus
	Septum
	Nucleus accumbens
IL-1	Pyramidal cell layer of the hippocampus
	Granule cell layer of the dentate gyrus
	Olfactory bulb
	Bed nucleus of the stria terminalis
	Substantia innominata
IL-1RA	Dentate gyrus
IL-2R/IL-2	Pyramidal cell layer of the hippocampus
	Granule cell layer of the dentate gyrus
IL-3R	Hippocampus
IL-3	Hippocampus
	Medial habenula
IL-6R/IL-6	Hippocampus
IL-8	Hippocampus
TNF-α	Hippocampus

4. NEUROIMMUNE COMMUNICATIONS VIA LIMBIC STRUCTURES

4.1. Lesioning Limbic Areas Affects Immune Responses

Lesions of the dorsal hippocampus or amygdaloid complex were found to produce a transient increase in splenocytes and thymocytes, as well as increased T-cell mitogen responses (Brooks *et al.*, 1982), and hypophysectomy was shown to reverse these effects (Cross *et al.*, 1982). Similarly, lesions of the hippocampus were found to cause differential effects on humoral immunity depending on the hippocampal fields and/or axonal pathways destroyed (Pan and Long, 1993). Alterations of cellular immune responses following small electrolytic lesions in different parts of the brain support the notion that the cingulate cortex, the central and the basomedial nucleus of the amygdala participate in the control of immunoneuroendocrine interactions (Masek *et al.*, 1992). Unilateral dopaminergic lesions of the nucleus accumbens have been shown to result in decreased splenic NK cell activity in left-lesioned mice as compared to right-lesioned animals, and unilateral striatal dopaminergic lesions have been found to impair the proliferation of splenic lymphocytes in the right-lesioned group only (Deleplanque *et al.*, 1994). These results suggest that immunologic reactivity is asymmetrically modulated by central dopaminergic pathways. Even though these data altogether show that structural disturbances within limbic areas affect immune functions, it should be kept in mind that, in view of the widespread and intimate relations of brain structures, results of experimental lesioning protocols should be interpreted with caution.

4.2. Neuroendocrine Immunomodulation at Limbic Neuronal Systems

As will be shown in the following, a number of recent experimental data strongly argue for an integration of limbic areas into immunoneuroendocrine circuits. Injection of IL-1β into the lateral cerebral ventricle reduced the affinity of hippocampal MRs in parallel to an enhanced HPA activity, and caused a shift in the MR/GR balance, which has been suggested to be of importance to the regulation of stress responses, behavioral activity, hippocampal excitability in general, long-term potentiation, and immune-induced neuroendocrine effects (De Kloet *et al.*, 1994; Schöbitz *et al.*, 1994b; McEwen and Sapolsky, 1995). It was concluded that this mechanism allows for an individual modulation of HPA axis activity during basal conditions, or in response to different amounts of stressful stimulation, including immune challenge. Another interesting aspect is that prenatal immune challenge has been shown to decrease MR and GR levels in the hippocampus of adult progeny, and to induce abnormalities in HPA axis function (Reul *et al.*, 1994). Furthermore, functional abnormalities in the HPA axis are often observed in pathological conditions, such as Alzheimer's disease, certain depressive illnesses, panic disorder, as well as multiple sclerosis (O'Brien *et al.*, 1993; Michelson *et al.*, 1994; Miller *et al.*, 1994;

Abelson and Curtis, 1996), and in major depression a hyperactivity of the HPA axis has been correlated with an enhanced IL-1β production (Maes *et al.*, 1993). In addition, recent studies addressing steroid hormone effects on neurons and behavior revealed a rich diversity of genomic and non-genomic steroid actions on neuronal properties (for review see Weeks and Levine, 1995). The work by Sapolsky (1986), Sapolsky and Pulsinelli (1985), Sapolsky *et al.* (1985, 1988, 1990)) e.g., pointed out the deleterious effects of prolonged glucocorticoid exposure on hippocampal neurons. On the other hand, a deficient immunoneuroendocrine feedback loop via the HPA axis has been implicated in animal models of spontaneous and experimentally induced autoimmune diseases (see above). In this context, an interesting recent study shows a number of immune abnormalities in transgenic mice expressing Type II GR antisense RNA comprising a deficient immunoneuroendocrine dialogue, alterations in thymocyte trafficking/migration, a shift of the T-cell balance towards the CD4 helper subset, and an absence of sex dimorphism in the development of GR mRNA expression and cell-mediated immunity (Morale *et al.*, 1995). Furthermore, Fischer 344 (F344) rats, which are known to mount a significantly higher corticosterone response to stress or to an immune challenge compared to Lewis and Sprague Dawley (SD) rats, are found to exhibit greater stress-induced Type II receptor activation in the cortex, hippocampus, and hypothalamus than SD and Lewis rats (Dhabhar *et al.*, 1995a). In addition, whereas Fischer rats serve as models for aging and cancer (Solleveld *et al.*, 1984; Ghanta *et al.*, 1990), Lewis rats are prone to autoimmune diseases (Sternberg *et al.*, 1989a, 1989b; Mason *et al.*, 1990). However, whether a defect in the hippocampal neuronal system is involved in the pathogenesis or exacerbation of autoimmune diseases needs to be clarified in future experiments.

In another approach to examine the effects of hippocampal IL-1 on brain functions, Linthorst *et al.* (1994) used a microdialysis probe, which allows stress-free intrahippocampal administration of recombinant human IL-1β (hIL-1β) in close vicinity of field CA3 and the dentate gyrus of rats. The intrahippocampal infusion of hIL-1β caused (i) a stimulation of HPA activity as reflected by increased plasma levels of ACTH, as well as plasma and dialysate levels of corticosterone; (ii) increases in hippocampal extracellular 5-HT levels in parallel with a decrease in behavioral activity; and (iii) an elevation of body temperature. The neural pathways mediating these effects need to be investigated further, but appear to involve serotonergic neurotransmission, possibly the nuclei raphe (Taylor, 1982; Werner and Bienek, 1985; Jacobs and Azmitia, 1992) and projections from hippocampus to nuclei raphe via septum (Swanson *et al.*, 1987; Cui *et al.*, 1993) or extended amygdala (Heimer, 1995e).

In further evidence of neuroimmunologic regulation exerted by limbic structures, Hauger *et al.* (1993) have shown the effects of high intracerebral levels of CRH on the regulation of CRH receptors in amygdala and anterior pituitary as well as on the modulation of immune functions. Chronic CRH pretreatment resulted in decreased CRH receptor concentrations exclusively in the amygdala, and splenic NK responses became insensitive to an acute intracisternal CRH injection. Although the central mechanisms of neuroendocrine–neuroimmune regulation are not yet known in detail, brain CRH (Irwin, 1994; Irwin *et al.*, 1987) and autonomic nervous system mechanisms (Irwin, 1994; Irwin *et al.*, 1990, 1992) have been shown to be implicated. Moreover, aside from different patterns of sympathetic dysregulation (Roy *et al.*, 1985; Rudorfer *et al.*, 1985; Veith *et al.*, 1994), in depression chronic CRH-hypersecretion has been reported (Nemeroff *et al.*, 1984, 1992), and reduced CRH binding-sites have been found in the frontal cortex (Nemeroff *et al.*, 1988). Both CRH activation and increased sympathetic nervous system activity may contribute to selective immune alterations observed in different types of depressive disorders. Supporting this view, Irwin *et al.* (1991) suggested that the activation of the sympathetic nervous system and elevated plasma levels of neuropeptide Y are associated with a reduction of NK activity in depressed patients. However, the interactions between neuropeptide Y, immunity, and depression appear to be rather complex, since central administration of neuropeptide Y also can result in immunoenhancing effects, as shown in the olfactory bulbectomized (OB) rat model of depression (Song *et al.*, 1996). A subchronic i.c.v. low-dose infusion of neuropeptide Y (i) reversed the deficit in NE concentrations in the amygdala of OB rats; (ii) decreased the concentrations of 5-hydroxyindole acetic acid (5-HIAA) in the hypothalamus; (iii) reduced hyperactivity of OB rats in the open field; (iv) elevated the concentrations of corticosterone; and (v) interestingly increased lymphocyte responses to phytohemagglutinin (PHA) and concanavalin A (ConA), which normally are suppressed in these animals, while not affecting the changes in the differential white blood cell count and the elevated PHA-induced chemiluminescence of mononuclear cells (Song *et al.*, 1996).

As AVP plays a significant role in the immunoneuroendocrine dialog (Nakatsuru *et al.*, 1991; Zelazowski *et al.*, 1993), it is of note that the amygdala, as well as the BST, contain AVP synthesizing cell bodies (De Vries *et al.*, 1985), and nitric oxide synthase has been detected in the amygdala (Pow, 1992). IL-2 has been shown to stimulate AVP release from hypothalamus and amygdala *in vitro* in a calcium-dependent manner, possibly via NO-mediated signaling (Raber and Bloom, 1994). Analogous *in vitro* results have been obtained regarding IL-2-induced CRH release from the hypothalamus as well as from the amygdala (Raber *et al.*, 1995), and it has been established that NE, as well as acetylcholine, enhances the *in vitro* release of CRH (Raber *et al.*, 1995) and AVP (Raber and Bloom, 1994) from the amygdala, involving NO-mediated signaling in the case of acetylcholine.

If limbic areas are in fact involved in the central regulation of the immunoneuroendocrine dialog, the exploration of the neurotransmitters involved in this issue will be of particular interest. Similar to results obtained in the hypothalamus, antigen challenge results in alterations of NE (Carlson *et al.*, 1987;

Zalcman *et al.*, 1991) as well as changes in 5-HT (Carlson *et al.*, 1987) in the hippocampus. Furthermore, dopamine levels in the nucleus accumbens were found decreased following administration of antigen at or about the time of peak immune responses (Zalcman *et al.*, 1991; Shanks *et al.*, 1994). Using *in vivo* microdialysis, Lacosta *et al.* (1994) detected an increase in extracellular dopamine in the nucleus accumbens following immunization. This *in vivo* dopamine elevation is a likely result of an increased release of dopamine from neurons. An interesting point is that immune-induced dopamine alterations in the nucleus accumbens appear to be more pronounced in isolated animals compared to animals housed in groups (Zalcman *et al.*, 1991; Lacosta *et al.*, 1994; Shanks *et al.*, 1994). Other studies have investigated cytokine-specific effects on monoamine activities. According to Zalcman *et al.*, 1994b), peripherally (i.p.) administered IL-1 increased NE turnover in the hypothalamus as well as in the hippocampus, and 5-HT turnover in the hippocampus and prefrontal cortex. IL-6 (i.p.) increased 5-HT activity in the hippocampus as well as the prefrontal cortex, and IL-2 (i.p.) induced a markedly increased hypothalamic NE utilization. All three cytokines modified dopamine activities in the prefrontal cortex (Zalcman *et al.*, 1994b), a brain region most sensitive to stressful stimulation (Roth *et al.*, 1988). Additionally, Zalcman's aforementioned study revealed intriguing results as (i) IL-1-induced increases of plasma corticosterone do not necessarily correlate with IL-1-induced alterations of hypothalamic NE activity; (ii) although IL-2 can markedly enhance NE utilization in the hypothalamus, this does not necessarily result in significant increases of plasma corticosterone concentrations; and (iii) even though IL-6 is able to alter central 5-HT and dopamine activities, it does not obligatorily affect hypothalamic NE activity or plasma corticosterone concentrations. The latter is in line with observations reported by Dunn (1992). The functional significance of these intricate relations will be considered below. Systemically, administered IL-2 also has been found to reduce the *in vivo* dopamine release from the nucleus accumbens (Anisman *et al.*, 1996). As for the amygdala, activation of dopamine D1 receptors has been shown to be involved in the selective enhancement of mitogen (ConA) responsiveness of splenocytes (Nistico *et al.*, 1994). Considering the organization of the basal forebrain cholinergic projections, which allow widespread influence on an array of brain regions, including hippocampus and amygdala (Rieck *et al.*, 1995), and recent investigations confirming the significance of cholinergic activity in learning and memory (Aigner, 1995; Sokolov and Kleschevnikov, 1995), the following data provide convincing evidence that cholinergic neurons in limbic areas have a crucial role in psychoimmunology. As recently summarized by Schauenstein *et al.* (1994), the cholinergic system modulates both immunologic reactivity and the immunoneuroendocrine dialog. Rinner and Schauenstein (1991) have reported that antigenic challenge results in a transient decrease of number and increase in affinity of muscarinic cholinergic receptors in the hippocampus. An important central action of IL-2 has been suggested to be involved in the modulation of hippocampal acetylcholine release (Hanisch *et al.*, 1993), which is in line with previous work by Araujo *et al.* (1989), who have observed that exogenous IL-2 diminished the potassium-evoked release of acetylcholine from rat hippocampal slices. Furthermore, systemically injected IL-1β was found to induce a decrease in extracellular acetylcholine in the hippocampus of freely moving rats (Rada *et al.*, 1991).

To summarize this section, it should be stressed that the hypothalamus is not the only site involved in the modulation of the pituitary–adrenal axis. Besides the evidence that the hippocampus indirectly modulates HPA activity (see above), the central and medial nucleus of the amygdala have been suggested to modulate ACTH secretion (Beaulieu *et al.*, 1986, 1987; Feldman *et al.*, 1994), and to exert differential effects on the CRH content in the ME (Beaulieu *et al.*, 1989; Feldman *et al.*, 1994). Although hypothalamic CRH neurons may be involved in such superior regulatory mechanisms exerted by limbic structures, it seems conceivable that neurosecretory fibers from the extended amygdala and/or hippocampus may project directly to the ME, forming an amygdalo/hippocampo-hypophysial pathway. It remains to be evaluated whether, how, or to what extent external signals (e.g. stress conditions including an immune challenge) are capable to induce the activation of such a route. Alternatively, a number of observations suggested the BST as a site of convergence conveying information from hippocampus and amygdala to hypothalamus or other parts of the brain (Cullinan *et al.*, 1993; Herman *et al.*, 1994; Pacak *et al.*, 1995), and the belief is held that this pathway is involved in the modulation of HPA activity (Dunn, 1987; Feldman *et al.*, 1990; Gray *et al.*, 1993) (Fig. 5). In line with the notion of additional regulatory mechanisms involved in the neuroimmune dialog, several data indicate that HPA axis activation is not an obligatory consequence following antigen challenge (Stenzel-Poore *et al.*, 1993; Shanks *et al.*, 1994). According to Zalcman *et al.*, 1994b) and Dunn (1992), peripheral cytokines not necessarily activate the HPA axis or affect plasma corticosterone concentrations, and results previously obtained in our own laboratory revealed that the corticosterone response induced by immunization with SRBC is abrogated following peripheral cholinergic treatment with physostigmine (Rinner and Schauenstein, 1991). Even though several trivial reasons, such as different experimental conditions or different dose-dependencies of antigen-specific immune responses, may account for such discrepancies, the available data clearly illustrate the high degree of complexity of central neuroendocrine immunomodulation.

4.3. Immune Stimulation Evokes Electrophysiological Changes in Neuronal Activities in Limbic Areas

A large body of information on neuroimmune communications and cognition has been generated by electrophysiological recordings of neurons. Besedovsky *et al.* (1977) were the first to demonstrate increased neuronal firing rates in the ventromedial

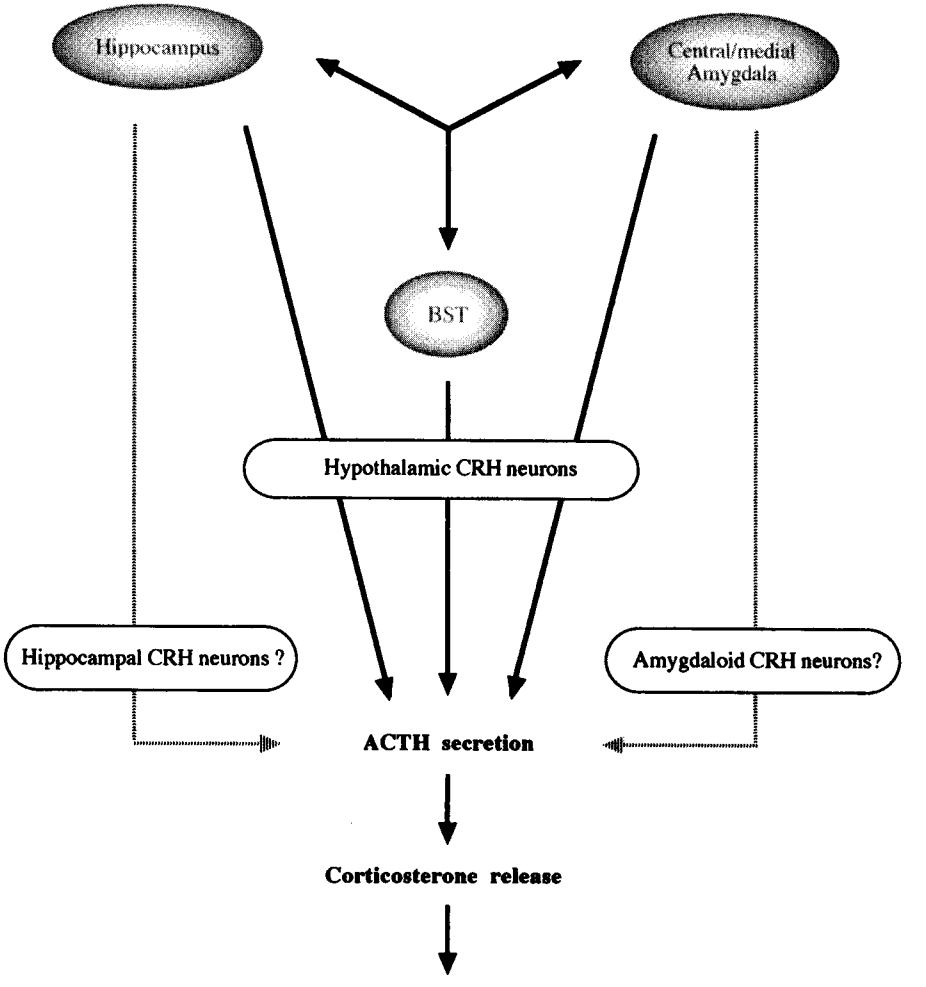

Fig. 5. Modulation of the pituitary–adrenal axis via hippocampus and amygdala. Abbreviations: BST, bed nucleus of the stria terminalis; CRH, corticotropin-releasing hormone; ACTH, adrenocorticotropin.

nucleus of the hypothalamus at the time of maximal antibody production following immunization. Similar results were obtained in the hippocampus (Korneva *et al.*, 1985). Recently, effects of immune-derived cytokines on electrophysiological phenomena in limbic areas have been described. IL-1β induced membrane hyperpolarization in neurons of the basolateral amygdala (BLA), most probably indirectly mediated through enhancement of endogenous GABA and accompanied by a decrease in input resistance (Yu and Shinnick-Gallagher, 1994). As stated in the same report, superfusion of IL-1β reduced the amplitudes of EPSPs (excitatory postsynaptic potentials) and blocked fast and slow IPSPs (inhibitory postsynaptic potentials) evoked by stimulation of the stria terminalis and the lateral amygdala possibly via presynaptic mechanisms. In a related study, IL-1β has been found to enhance GABAergic IPSPs in hippocampal neurons of the pyramidal cell layer (Zeise *et al.*, 1992), which would suggest contrary cytokine effects in different brain regions, but could also be due to different experimental approaches used in these two studies. Furthermore, IL-1β was shown to have excitatory effects on BST neuronal activity possibly via prostaglandin mobilization (Wilkinson *et al.*, 1993), and both IL-1β (Plata-Salamán and Ffrench-Mullen, 1992) as well as IL-2 (Plata-Salamán and Ffrench-Mullen, 1993) depress voltage-dependent calcium currents in CA1 hippocampal neurons.

It has long been established that learning and memory is related to plastic changes of neuronal pathways, and long-term potentiation (LTP) of synaptic transmission is a widely used model of neuronal plasticity (Bliss and Collingridge, 1993). Cytokine effects on electrically induced potentiation of the synaptic transmission have been primarily described in the hippocampus. Interferons have been shown to inhibit the induction of LTP and to attenuate post-tetanic potentiation (PTP), short-term potentiation (STP) as well as the LTP maintenance phase (D'Arcangelo *et al.*, 1991). IL-2 inhibited the induction of both LTP and STP, attenuated PTP and reduced the maintenance of LTP (Tancredi *et al.*, 1990). Tumor necrosis factor affected LTP negatively (Tancredi *et al.*, 1992), and IL-1β inhibited the

potentiation of synaptic transmission in field CA3 of mouse (Katsuki *et al.*, 1990), as well as in field CA1 of rat hippocampal slices (Bellinger *et al.*, 1993). The underlying mechanisms of cytokine-induced effects on LTP remain to be further clarified, but may include NMDA (Collingridge and Davies, 1989; Bashir *et al.*, 1991) and muscarinic receptors (Burgard and Sarvey, 1990; Sokolov and Kleschevnikov, 1995), the protein kinase C system (Farrar and Andersen, 1985; Hu *et al.*, 1987; Malinow *et al.*, 1988; Reymann *et al.*, 1988), sphingosine-sensitive processes (Malinow *et al.*, 1988; Ballou, 1992; Kolesnick and Golde, 1994), the G protein system (Evans *et al.*, 1987; Goh and Pennefather, 1989; Harnett and Rigley, 1992), as well as endogenous NO (Schuman and Madison, 1991; Watanabe *et al.*, 1995b). Besides mono- and lymphokines, several growth factors have been shown to influence the generation of LTP. Both epidermal growth factor and basic fibroblast growth factor were found to promote hippocampal LTP either in fimbria–fornix-lesioned rats or anaesthetized rats (Ishiyama *et al.*, 1991; Abe *et al.*, 1992). Finally, it should be considered that induction criteria for LTP are not only studied in the hippocampal formation but also in other limbic parts of the brain. Recently, it was suggested that neuronal activities in the ipsilateral BLA are required in part for the induction of LTP in the dentate gyrus *in vivo* (Ikegaya *et al.*, 1995). Moreover, recent work supports the hypothesis of a cooperation of hippocampal formation and amygdala providing electrophysiological evidence of direct neuronal connections between the BLA and the dentate gyrus (Ikegaya *et al.*, 1996).

4.4. Limbic Structures in Stress and Immunity

With the emergence of interdisciplinary research areas, such as psychoneuroimmunology, new insights into the concept of stress as a stereotyped and non-specific response (alarm, resistance, exhaustion) to aversive or noxious stimuli were obtained, indicating the involvement of an array of regulatory mechanisms including corticosteroids, monoamines, acetylcholine, endogenous opioids, melatonin, several pituitary hormones and cytokines (Khansari *et al.*, 1990; Hoffman-Goetz and Pedersen, 1994). As initially mentioned, it is generally accepted that different stressors alter immunity in different ways, and this research is reviewed in detail elsewhere (Dantzer and Kelley, 1989; DeGiorgi and Altomare, 1992; Rinner *et al.*, 1992; Fricchione and Stefano, 1994; Irwin, 1994; Kort, 1994; Dhabhar *et al.*, 1995b). Noteworthy in this regard is an intriguing finding, which suggests that the adrenal gland may be the source of plasma IL-6 following exposure to physical and psychological stressors, and that β-adrenergic receptor stimulation is not involved in mediating this effect (Zhou *et al.*, 1993). Basal IL-6 secretion in cultures of splenic cells and peripheral blood mononuclear cells was not enhanced after repeated footshocks, and mitogen-induced IL-6 production was decreased in cultures of immune cells following stress. Thus, the elevation of plasma IL-6 may reflect a hormonal response of the organism to arousal. Whether psychosocial stress influences the expression of cytokine mRNA and/or cytokine synthesis in limbic areas is not yet clear. With the exception of Pousset *et al.* (1996) (see also above), who recently observed the induction if IL-6, TNF-α and transforming growth factor β (TGF-β) mRNA expression in cultured rat hippocampal astrocytes by low concentrations (10^{-10}–10^{-12} M) of serotonin, non-inflammatory stimuli appear to induce IL-1β gene expression in the hypothalamus exclusively (Minami *et al.*, 1991). Endogenous glucocorticoids are known to modulate the central effects of cytokines (Morrow *et al.*, 1993a; Goujon *et al.*, 1995). However, studies addressing the mechanisms and the specific site of action are rather limited to date. Despite such gaps in our knowledge, a considerable number of data describe relations between stress effects including levels of catecholamines in blood and different nuclei of the amygdaloid body on the basis of lesion or stimulation experiments (Henke, 1980a, 1980b, 1985; Johansson *et al.*, 1981; Galeno and Brody, 1983; Morrow *et al.*, 1993b). Electrolytic lesions of the central nucleus of the amygdala attenuated the increase in dopamine turnover in the frontal cortex normally seen following mild stress (Davis *et al.*, 1994). The question of the underlying neural pathways mediating this reponse is not resolved. However, dopaminergic cells in the ventral tegmental area, which in turn project to the prefrontal cortex may be involved (Maeda and Mogenson, 1981; Wallace *et al.*, 1992). CRH–NE interactions at the central nucleus of the amygdala appear to mediate gastric cytoprotective effects during stress implicating β-adrenoceptor action (Ray *et al.*, 1993). An increase in NE levels also was observed in the BST of rats during 2 hr of immobilization (Pacak *et al.*, 1995). In another study, an increased number of CRH-binding sites was found in the amygdala of tree shrews following psychosocial stress (Fuchs and Flügge, 1994). Kalin *et al.* (1994) have observed that restraint stress increased levels of CRH mRNA in the rat amygdala. However, a more recent study failed to replicate this result, and it was suggested that type or duration of stressors and species differences may account for selective responses of CRH neurons in the amygdala (Makino *et al.*, 1995). Support to this notion came from other studies, indicating that different neuronal networks, particularly dopaminergic activity in the nucleus accumbens, are involved in the adaptation to aversive or pleasurable repeated experiences (Le Moal and Simon, 1991; Imperato *et al.*, 1992). The concept that increased dopamine turnover, metabolism and release in mesocorticolimbic areas is a strain-specific and time-dependent response to stress-inducing stimuli, such as physical restraint, footshock, or social defeat stress, has been experimentally confirmed by a number of investigations (Cabib *et al.*, 1988; Roth *et al.*, 1988; Abercrombie *et al.*, 1989; Puglisi-Allegra *et al.*, 1991; Tidey and Miczek, 1996). Furthermore, it is well established that the hippocampus, particularly the hippocampal cholinergic system, has a crucial role in the processing of stressful stimuli (Finkelstein *et al.*, 1985; Gilad *et al.*, 1985; Tajima *et al.*, 1996). Chronic psychosocial stress also has been found to induce morphological alterations in CA1 and CA3 hippocampal pyramidal

neurons of tree shrews (Fuchs *et al.*, 1995). However, the functional relationship between stress-induced HPA axis activation and abovementioned neuronal systems is still a point of debate. Imperato *et al.* (1991) e.g. have observed in rats that restraint stress and freeing the animals both stimulated release and metabolism of dopamine in the nucleus accumbens and prefrontal cortex, as well as the release of acetylcholine in the hippocampus. After habituation to the respective situation these alterations declined. Corticosterone levels were elevated during the whole period of restraint stress and decreased by freeing the animals. Moreover, this study provides evidence that these dopamine and acetylcholine changes in limbic structures occur independently of HPA axis activation. Thus, different forms of stressful stimulation appear to be processed in limbic brain regions implicating emotional experiences, and selective neurochemical changes in limbic structures in turn may cause selective central and peripheral neuronal, neuroendocrine and, most probably, immune alterations.

A final point to be discussed is that brief or prolonged periods of stress have been shown to influence memory formation in different ways (reviewed by McEwen and Sapolsky, 1995). Considering glutamate receptors as putative candidates involved in learning and memory (Advokat and Pellegrin, 1992; Aigner, 1995), changes in excitatory amino acid receptor binding have been demonstrated in the hippocampus following different qualities of stressful stimulation (single social stress experience, acute tail-shock stress) (Tocco *et al.*, 1991; Krugers *et al.*, 1993). However, contrary results were obtained in response to repeated restraint stress (Watanabe *et al.*, 1995a). Further detailed research is needed to study the implication of glutamate receptors in stress responses and cognition, and future experiments should examine the specific role of these receptors in alterations of immune responses in association with psychosocial stress. Even though, at present, nothing is known about such an interaction, first — albeit indirect — lines of evidence appear to point in this direction. In experiments on embryonic mammalian hippocampal neurons, Mayer and Vyklicky (1989) observed that the T-cell mitogen ConA selectively reduces desensitization of quisqualate receptors. The most compelling evidence for an interaction between limbic structures, the glutamatergic system and the immune system is found in a recent report by Hardin-Pouzet *et al.* (1996). The authors described an enhanced expression of glutamate dehydrogenase in cultured hippocampal astrocytes following treatment with TNF-α or IL-1α. This enzyme is involved in glutamate metabolism and helps to maintain a low (non-toxic) extracellular glutamate concentration.

4.5. Effects of the Activated Immune System on Limbic Structures

Consistent with the notion of a link between limbic areas and immunity, peripheral endotoxin (LPS) treatment has been found to result in decreased ^{125}I-IL-1α binding in the hippocampus (Takao *et al.*, 1994) and dentate gyrus (Haour *et al.*, 1990). Furthermore, LPS, IL-1α or β can increase prostaglandin (PG)E2 biosynthesis in the dorsal hippocampus of mice involving IL-1 receptor activation (Weidenfeld *et al.*, 1995), and LPS decreases the affinity of hippocampal MRs (Schöbitz *et al.*, 1994b). The LPS-induced increases in 5-HT metabolism in the hypothalamus and hippocampus can be asymmetrically expressed (Delrue *et al.*, 1994), supporting observations on brain and behavioral lateralization, which have been associated with immune reactivity (review by Neveu, 1992). Central LPS has been found to induce different patterns of cytokine mRNA expression in the brain including the hippocampus (De Simoni *et al.*, 1995). In addition to what has been observed with bacterial endotoxin, muramyl dipeptide, a microbial product with adjuvant activity, which has been shown to be implicated in steep regulation (Krueger and Majde, 1995), can alter neuronal activity in the hypothalamus as well as the hippocampus (Dougherty and Dafny, 1990).

Immunologic reactivity also can interfere indirectly with the production of neurotransmitters, and could have neurobiological as well as psychological consequences within limbic structures. Werner-Felmayer *et al.* (1989) have found that an IFN-γ-induced pteridine biosynthesis is associated with an enhanced tryptophan metabolism to form kynurenine. This reduces the availability of 5-HT and may cause the production of metabolites with neurotoxic properties. In this context, a chronically activated immune system, as is observed in HIV patients, has been correlated with reduced serum levels of tryptophan (Fuchs *et al.*, 1990) and with decreased whole blood levels of 5-HT (Launay *et al.*, 1989). Interestingly, both results have been shown to be associated with neurologic/psychiatric symptoms in HIV patients.

Additional evidence that HIV infection affects limbic areas came from studies in rats. The i.c.v. infusion of recombinant gp120, as well as injection directly into the dorsal hippocampus, induced IL-1 activity in the brain (Sundar *et al.*, 1991), whereby the injection into the hippocampus was more effective than i.c.v. infusion. This was associated with an enhanced HPA axis activity, reduced NK cell activity and lymphocyte mitogen responses.

Finally, immune cell-derived cytokines were found to exert effects on growth and survival of neurons. Hippocampal neurons, as well as glial cells, respond to IL-1 stimulation in culture by enhanced production of nerve growth factor (NGF) (Friedman *et al.*, 1990; Spranger *et al.*, 1990) and i.c.v. injection of IL-1 was found to increase NGF mRNA in the hippocampus (Spranger *et al.*, 1990). Recombinant IFN-γ has been reported to promote the differentiation of cultured embryonic hippocampal neurons at physiologically relevant concentrations (Barish *et al.*, 1991). Additional lines of evidence indicate that IL-6 acts as a neurotrophic factor (Hama *et al.*, 1989, 1991; Kushima and Hatanaka, 1992; Kushima *et al.*, 1992). Moreover, IL-6 has been recognized to protect cultured rat hippocampal neurons against glutamate neurotoxicity (Yamada and Hatanaka, 1994), which has been suggested to be caused, in part, by NMDA receptor/channel activation (Rothman and Olney, 1987; Yamada and Hatanaka, 1994). This is in agreement with Toulmond *et al.* (1992)'s *in vivo* findings in rats regarding a neuroprotective role of

IL-6 against neurotoxic effects of NMDA on striatal cholinergic neurons. Sarder *et al.* (1996) observed differential effects of IL-2 and IL-6 on neuronal morphology and neurite regeneration in cultured hippocampal cells. IL-2 promoted both elongation and branching of neurites, whereas IL-6 only promoted elongation of neuronal processes. Furthermore, IL-2 significantly increased the number and the length of the branches, which emerge from the proximal part of a damaged neurite, and it also increased the total length and number of non-damaged neurites. In contrast, IL-6 did not show any significant effect on these parameters in laser beam-damaged neurons. In all, the results of the present and preceding studies clearly indicate that immune-cytokines selectively affect neuronal growth, survival and neuritogenesis. On the other hand, direct actions of cytokines, or interactions between cytokines and neurotrophic factors may have detrimental effects on limbic neuronal systems. Besides NGF, one of the best known neurotrophic factors is brain-derived neurotrophic factor (BDNF). Both of them have been considered as agents that presumably act on cholinergic neurons of the basal forebrain (Whittemore and Sieger, 1987; Phillips *et al.*, 1990) and, because of this, probably are able to protect neurons from neurodegenative diseases. In this context, Lapchak *et al.* (1993) reported that systemic IL-1β decreases BDNF mRNA expression in the rat hippocampal formation, and this mechanism is thought to be involved in the neuropathology of Alzheimer's disease. Chronic treatment with recombinant IL-2 has been used to determine the cytokine effect on the CNS of aged mice as compared to adult animals (Nemni *et al.*, 1992). IL-2-mediated neuronal cell losses and degenerative changes limited to hippocampal regions became apparent in aged mice only, and were correlated with mnestic dysfunctions.

4.6. Conditioning of Immune Functions — Mediated Via Limbic Areas?

Based on the work of Pavlov (1928), conditioned neutral stimuli, such as saccharin, lithium chloride or environmental stimuli, that were previously paired with an unconditioned stimulus, e.g. an immunosuppressive drug, subsequently are able by themselves to modulate an immune response (conditioned response). A detailed review of this issue is presented in Ader and colleagues' *Psychoneuroimmunology* (1991) — the underlying mechanisms mediating these phenomena remain largely speculative. Endogenous increases of glucocorticoids caused by stressful conditioning paradigms may be involved in conditioned immunosuppression (Kelley *et al.*, 1985; Lysle *et al.*, 1988). However, other studies did not support this hypothesis (Ader *et al.*, 1979; King *et al.*, 1987; Peeke *et al.*, 1987). Endogenous opioids, such as β-endorphin, and the HPA axis, are believed to play an essential role in the conditioned enhancement of NK cell activity (Hsueh *et al.*, 1994, 1995). In line with this view, arecoline, a muscarinic cholinergic agent, which previously has been shown to stimulate HPA activity via central pathways (Calogero *et al.*, 1989), has recently been identified as a drug that serves as an unconditioned stimulus in a Pavlovian conditioning paradigm (Demissie *et al.*, 1995). The pairing of arecoline with a novel odor (camphor) could be used to trigger a conditioned response, whereby the subsequent exposure to the odor alone was sufficient to raise NK activity. In a related study, centrally injected IFN-β also has been found to serve as an unconditioned stimulus for the conditioning of an NK cell response (Solvason *et al.*, 1993); however, the central pathways mediating this effect still remain to be examined. Other data suggest the involvement of endogenous CRH (Perez and Lysle, 1995), and the β-adrenergic system (Lysle *et al.*, 1991; Luecken and Lysle, 1992) in the conditioned modulation of different types of immune responses. Whether and how limbic areas actually participate in the central modulation of conditioned immune responses is not yet formally known. Evidence in favor of this notion came from a study by Pezzone *et al.* (1992). An auditory cue as conditioned stimulus following electric footshock (the unconditioned stimulus) was able to induce Fos expression in different parts of the brain including the medial amygdaloid nucleus. In addition, both of these stimuli were capable to suppress immune functions. Unfortunately, it cannot be excluded that Fos activation in the amygdala just reflects the role of this structure in an (un)conditioned fear response. Thus, these studies should be extended by using non-aversive conditioning paradigms. However, based on the data summarized herein, and in view of the well-known role of limbic areas in learning processes, as well as in the processing of associative emotional factors, we propose that neuronal activities in the hippocampal formation and extended amygdala are critically involved in these phenomena.

5. CONCLUSIONS

In this review, we have charted for the first time an integrated view of the neuroanatomy of psychoimmunology based on the description of afferent/efferent pathways in the neuroimmune dialog, as well as on the major functions of limbic areas and their putative roles in brain–immune communications. It stands to reason that psychoneuroimmunology cannot provide a universal explanation of a given disease, but it may enhance our understanding of psychosomatic aspects of immune disorders, such as immune deficiency states or autoimmune diseases. Additionally, it may open up new pathophysiological concepts of different types of depression and dementia. However, considering the conspicuous complexity of neuronal networks and neuroendocrine mechanisms on the one hand, and the complexity of immune functions on the other, it is not surprising that the results obtained are diverse and often contradictory. We can only conclude that (i) humoral and neural, most probably vagal, afferents link the peripheral immune system with the brain; (ii) humoral and neural efferents, such as the HPA axis, a number of neuropeptides and autonomic pathways link the CNS with the peripheral immune system; (iii) limbic structures represent the neuroanatomical substrates for psychoimmunomodulation as they serve as superior regulators of neuroendocrine and

autonomic centers allowing an individual and selective modulation of learning processes, memory, emotional behavior, stress and immune responses.

Given these results, immune dysfunctions may (i) arise from a dysregulation of the parasympathetic division of the nervous system; (ii) from an MR/GR imbalance in the hippocampus leading either to an enhanced or an impaired HPA activity; (iii) from changes in number, affinity or signaling of cytokine receptors in the CNS; and (iv) from alterations in release and turnover of all the neurotransmitter material mentioned, ranging from NE to excitatory amino acids. More detailed knowledge of the pharmacology, particularly of the "newcomers" of transmitters, as well as their physiological roles in brain and immune functions, will be required to clarify further the extensive network of brain–immune interactions. Additional studies at the molecular level will be needed to determine precisely cytokine effects on neurotransmission. Cholinergic and GABAergic responses should be studied in more detail. Finally, a potential field of interest would be the investigation of glutamatergic mechanisms in neuroimmunology. Such investigations should lead to a better understanding of neuroimmunomodulation at limbic structures to provide the scientific basis to Juvenal's "*Orandum est ut sit mens sana in corpore sano*".

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