Update in Intensive Care and Emergency Medicine

Brain Failure

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Edited by

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With 60 Figures and 31 Tables

Springer-Verlag Berlin Heidelberg New York
London Paris Tokyo Hong Kong

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ISBN 3-540-51655-7 Springer-Verlag Berlin Heidelberg New York
ISBN 0-387-51655-7 Springer-Verlag New York Berlin Heidelberg

Library of Congress Cataloging-in-Publication Data
Brain failure / edited by D. Bihari and J.W. Holaday
(Update in intensive care and emergency medicine: 9)
ISBN 0-387-51655-7 (U.S.: alk. paper) 1. Brain--Wounds and injuries--Complications and sequelae. 2. Brain--Pathophysiology. I. Bihari, David, 1954- II. Holaday, John W. III. Series. [DNLM: 1. Brain Diseases. W1 UP66H v. 9 / WL 348 B8143] RD594.B72 1989 616.8'047--dc20 89-21827

Typesetting and printing: Zechnersche Buchdruckerei, Speyer
Bookbinding: J. Schäffer, Grünstadt

2119/3140-543210 - Printed on acid-free paper

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Brain, Endocrine and Immune Interactions: Implications in Intensive Care*

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Introduction

With the trend to specialize in medicine and biomedical research, the body has been studied as a series of individual systems; this has afforded us a wealth of detailed knowledge at the system level, but often at the expense of a functional knowledge of the whole. Within the past few years, important functional links among the brain, endocrine and immune systems have been demonstrated to play a role in the intact organism's adaptive and maladaptive responses to injury and disease. Precise knowledge about the interactions among these networks may allow for exciting new therapeutic strategies with direct relevance to the practice of critical care and emergency medicine.

Chronic responses to the physiological stress of injury or disease include marked changes in the regulation of neuroendocrine function by the brain, pituitary and target glands, and often include a sustained elevation of circulating glucocorticoids and the reduced secretion of gonadotropins, thyroid stimulating hormone, prolactin and growth hormone in the plasma [1–3]. The hormones are known to play important roles in the regulation of growth, reproduction and metabolism, all of which may affect survival. Recent observations by our group and others suggest that regulation of immune host defenses should be included in the list of events mediated by neuroendocrine hormones; thus, changes in neuroendocrine status following critical illnesses or injury may contribute to the coincident immunologic dysfunction which is often observed. Brain/endocrine/immune interactions, however, are not unidirectional, e.g. the release of monokines (interleukin-1 [IL-1]) or tumor necrosis factor (TNF) from macrophages, as part of immunological responses to infection or inflammation, may also affect brain and neuroendocrine function. Furthermore, other cytokines, such as colony stimulating factor (CSF), may act upon macrophages or brain microglial cells ("macrophages of the brain") to release substances that stimulate neuronal growth in vitro. Many of the drugs routinely used for the treatment of critical illnesses or injury have profound effects upon the immune system by actions at

* The views of the author(s) do not purport the position of the Department or the Department of Defense, (para 4-3, AR 360-5).
Research was conducted in compliance with the Animal Welfare Act and other Federal statutes and regulations relating to animals and experiments involving animals, and adheres to principles stated in the 'Guide for the Care and Use of Laboratory Animals', NIH publication 86-23, 1985 edition.

various levels of the brain/endocrine/immune axis. The effects of glucocorticoids on immune responses are well recognized [4]; however, the immunological responses to drugs that alter the release of other hormones, including dopamine, metoclopramide, haloperidol, morphine, mucolytics, cyclosporine and other pharmacological agents commonly used in critical care and emergency medicine, have not been appreciated. Below, we will review evidence that pharmacological manipulation of the brain/endocrine/immune axis results in many effects that are of potential relevance to clinicians involved in intensive care or emergency medicine.

These studies emphasize our own work defining:

1. the importance of prolactin (PRL) as an immunopermissive hormone based on studies with hypoprolactinemic animals and on the production of immunoreactive/prolactin (ir-PRL) by cells of the immune system;
2. chronic morphine treatment as a "pharmacologic stressor",
3. the ability of PRL to reverse both morphine and glucocorticoid-induced immunosuppression;
4. the effects of immune cell products (e.g. interleukin-1) on the release of PRL and other pituitary hormones; and
5. the effects of cytokines on nerve cell growth and differentiation.

T-Cell-Dependent Immunity Is Compromised by Hypoprolactinemia

In Vivo Studies

Prolactin is a peptide hormone classically associated with lactation and the reproductive cycle; however, the evolutionary history of prolactin research has revealed that this fascinating molecule subserves many additional physiological functions in vertebrates (for review, see [5]). Although prolactin shares some structural similarity and biological actions with growth hormone (GH) and placental lactogen (PL), prolactin acts upon its own receptors to result in many trophic, metabolic, endocrine and immunologic actions.

The release of prolactin from pituitary lactotrophs in vivo varies according to time of day and is further modulated by behavioral and environmental stimuli, the reproductive cycle, steroid hormones, immunoregulatory cytokines and various drugs (Table 1). Among the primary neuroendocrine processes involved in regulating circulating levels of this hormone, prolactin secretion is tonically inhibited by the release of dopamine from the tuberoinfundibular dopaminergic neurons into the portal bloodstream to act upon dopamine-2 (DA-2) receptors located on lactotroph cells of the anterior pituitary. At the cellular level, DA-2 receptor-mediated inhibition of adenylate cyclase results in decreased cyclic AMP (as well as changes in Ca^{++} flux) and, ultimately, decreased prolactin release [5, 6]. The opposite effect occurs when dopamine antagonists, such as metoclopramide or haloperidol, are used; thus, inhibition of this dopaminergic system by dopamine antagonists results in prompt prolactin secretion. In healthy drug-free individuals, once released into the circulation, prolactin exerts ne-

Table 1. Potential immunological effects of drugs commonly used in critical care and emergency medicine

Drug	Drug type	Endocrine effect	Immunological effect	Site of action
Dopamine Bromocryptine	DA-agonist	↓ Prolactin	Immunosuppression	T-cell
Haloperidol Metoclopramide	DA-antagonist	↑ Prolactin	Immunostimulation	T-cell
Morphine (chronic)	Opioid agonist	↑ Corticosterone ↓ Prolactin	Immunosuppression	Same sites as glucocorticoids
Cysteamine	Mucolytic	↓ Prolactin	Immunosuppression	Reducing agent ↓ prolactin T-cell

gative feedback control to regulate its own release by stimulating these dopaminergic neurons, restoring once again the dopaminergic inhibitory tone [6].

As predicted by the neuroendocrine system described above, the pharmacological administration of DA-2 agonists (e.g. dopamine or bromocryptine) suppresses prolactin release, whereas centrally or peripherally-acting neuroleptic or antiemetic DA-2 antagonists (e.g. haloperidol and metoclopramide respectively) promptly stimulate prolactin release by blocking endogenous dopaminergic tone. In the critical care setting, we suggest that the use of dopamine infusions to maintain hemodynamic and renal function may contribute to the compromised immunological function and anergic status of patients (see conclusions). Conversely, the use of haloperidol or metoclopramide may improve immune function.

Growth hormone may also play an important role in the regulation of host defenses [7, 8]. Pharmacologically, there is a key difference between the regulation of pituitary prolactin and growth hormone secretion. Although prolactin secretion can be totally inhibited by direct actions of dopamine or any drug with dopaminergic actions at pituitary DA-2 receptors, dopamine agonists stimulate secretion of pituitary growth hormone by actions upon the brain's neuroendocrine pathways [6]; thus, certain pharmacologic means of inhibiting prolactin secretion, either experimentally or clinically, have no effect on growth hormone secretion. Both prolactin and growth hormone secretion, however, tend to be increased by estrogens and inhibited by glucocorticoids [5].

Secretion of both hormones is increased acutely by stress in humans, but secretion appears to attenuate rapidly with chronic stress. Sustained stress greatly inhibits prolactin secretion in response to subsequent stimuli acting at a suprapituitary level (e.g. the superimposition of an acute stress or opiates) [9–11]. One key question as yet unresolved is whether primate growth hormone, which binds with high affinity to both growth hormone and prolactin receptors to produce lactation, can or cannot mimic the immunopermissive effects of prolactin described below; this is in contrast to non-primate growth hormone that does not bind to prolactin receptors or produce lactation. Nonetheless, from animal experimentation, we would predict that alterations in prolactin secretion in chron-

ically stressed individuals may, along with stress-induced increases in circulating adrenal corticosteroids, be an important co-determinant of changes in immune function associated with adaptation to chronic stress, such as critical illnesses.

The history of evidence to specifically link prolactin with immune function is relatively recent. In 1983, Nagy et al. reported that the drug bromocryptine, a dopamine agonist which inhibits prolactin secretion, suppressed antibody formation to sheep red blood cells and the delayed hypersensitivity response in rats [12]. The effect was blocked by coincident treatment with prolactin; however, little was known about the precise mechanisms by which prolactin exerted its immunological actions.

We have recently shown that suppression of prolactin secretion in mice with bromocryptine:

1. increases the lethality of an infectious challenge with Listeria monocytogenes,
2. abrogates T-lymphocyte-dependent activation of macrophages, as well as the production of lymphocyte interferon following inoculation with Listeria or mycobacteria (Fig. 1),
3. suppresses T-lymphocyte proliferation without affecting the production of interleukin-2.

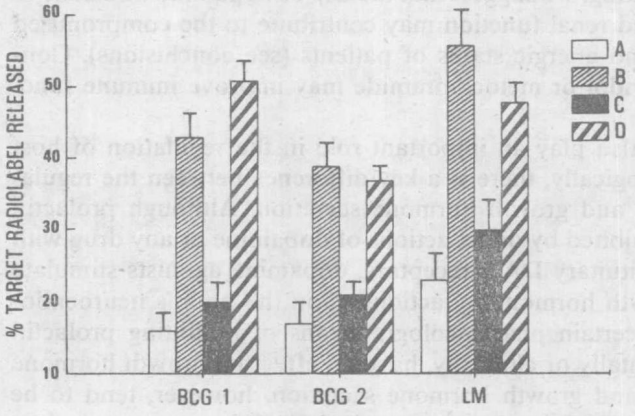

Fig. 1. Effects of bromocryptine on the induction of activated, tumoricidal macrophages during Mycobacterium bovis (BCG) or L. monocytogenes (LM) infection. Adherent peritoneal cells from groups of C3H/HeN male mice, including controls (A-unactivated macrophages from animals that were not inoculated) or from two separate studies of animals inoculated intraperitoneally with viable M. Bovis, strain BCG (BCG 1, BCG 2) or with LM 10 days previously were cultured with radiolabeled TU-5 tumor target cells. Groups of 5 mice each were treated on days 1 to 4 with daily injections of either: (B) vehicle, (C) bromocryptine mesylate (200 micrograms in 0.2 ml vehicle) (D) bromocryptine 200 micrograms and ovine prolactin (100 micrograms in 0.1 ml vehicle). Tumor cytotoxicity was estimated by measurement of radiolabel release in triplicate cultures at 48 h and expressed as percent of total tumor-cell radiolabel. Note that the activation of macrophages by inoculation with either BCG or LM (columns B) above control values (columns A) was blocked by bromocryptine coadministration (columns C) and this was reversed by bromocryptine plus prolactin (columns D). See [8] for details

All of the changes can be prevented by coincident administration of ovine prolactin [13]. Results in experimental animals demonstrate that hypoprolactinemia produced by dopamine agonists compromises host defenses by preventing T-cell production of macrophage activating factors and preventing T-cell proliferation [13].

Cysteamine is a dithiol reducing agent which is used as a mucolytic, as an antidote for acetaminophen overdose and for the treatment of nephropathic cystinosis. Cysteamine inactivates prolactin by cross-linking sulfhydryl bonds, a mechanism distinct from the neuroendocrine inhibition of pituitary prolactin secretion by dopamine agonists described above. As further evidence for the role of prolactin in immune function, cysteamine appears to selectively inactivate prolactin, but not its molecular cousin, growth hormone. We demonstrated that mice made hypoprolactinemic by cysteamine HCI treatment were as immunosuppressed as bromocryptine-treated mice [14]. Measurement of circulating prolactin levels in mice treated with varying doses of cysteamine demonstrated a positive correlation between the level of prolactin and lymphocyte proliferation in response to the mitogen, concanavalin-A (Con-A). As before, immunocompetence was restored by the administration of exogenous prolactin [14]; thus, two separate lines of experimental evidence point to the importance of prolactin in T-cell immunity and indicate that hypoprolactinemia comprises host defenses.

Additional studies have shown that the in vivo administration of exogenous prolactin or dopamine antagonists such as metoclopramide, which stimulate secretion of endogenous prolactin, resulted in significant increases in lymphocyte proliferative responses to mitogens in immunocompromised mice; these treatments were also found to reverse immunosuppression produced by administration of the drug cyclosporine (unpublished observation, Bernton EW, Bryant HU, Holaday, JW). Results from the laboratories of Russell and colleagues [15] have indicated that prolactin and cyclosporine may mutually compete for binding sites on lymphocytes; thus, the immunosuppressive actions of cyclosporine may, in part, be a consequence of its actions to inhibit prolactin's immunostimulatory effects by blockade of the prolactin receptor. As mentioned below, prolactin also reverses immunosuppression due to elevated clycocorticoids or chronic morphine treatment in mice. Although the collective evidence strongly indicates that prolactin stimulates immune function, prolactin cannot be considered to function as an immunostimulant per se, since hyperprolactinemia does not enhance immune function above control levels; instead, it appears to be an important counter-regulatory hormone that can oppose the immunosuppressive actions of stress or of drugs such as cyclosporine, morphine or glucocorticoids.

In Vitro Studies

Several reports indicate that lymphocytes may function as "neuroendocrine systems" in microcosm. Since lymphocytes are themselves capable of producing many of the hormones primarily associated with the anterior pituitary [8], we looked for evidence that lymphocytes may also produce a prolactin-like protein.

Immunocytochemical studies using monoclonal antibodies specific for prolactin (but not growth hormone) demonstrated that, following mitogenic stimulation with Con-A, phytohemagglutinin or antibody to the T3 receptor, a large subpopulation of human or murine lymphocytes accumulate prolactin-immunoreactive (ir-PRL) material within [16]. We and others [17] have also documented the production of ir-PRL using western blots of electrophoretically separated proteins from lymphocyte lysates or supernatants [16, 18]. Ir-PRL appears to play a critical role in lymphocyte proliferation. Specifically, low dilutions of antisera to prolactin-inhibited proliferation of mouse and human lymphocytes, as well as transformed lymphocytic cells responsive to T- and B-cell growth factors. The inhibitory activity could be affinity-adsorbed from the antisera by purified prolactin [19]; thus, prolactin or a prolactin-like protein may be a cytokine produced in an autocrine manner by proliferating cells of lymphoid and possibly other lineages [20]. The studies raise the interesting question as to the immunoregulatory role of pituitary prolactin secretion if a similar protein can be produced to act in an autocrine fashion by immune cells.

Chronic Morphine Treatment and Immunosuppression

It has long been known that heroin addicts are more susceptible to infectious disease, which is at least partially attributable to a compromised immune function in addition to the obvious shared use of paraphernalia [21, 22]. Of course, morphine or similar opiate drugs are extensively used for pain management in critically ill or traumatized patients. The use of morphine for its desired analgesic effects may have undesirable actions, such as immunosuppression, that may contribute to the anergy of critical illnesses.

We observed that chronic administration of morphine to mice, via a pellet implant model classically used to illustrate tolerance to the analgesic effects of morphine, resulted in atrophy of the spleen and thymus and suppressed blastogenic responses of splenocytes to both T- and B-cell mitogens (Fig. 2) [23]. Chronic exposure to morphine in this manner also suppressed macrophage responses [24], interleukin-2 production [25] and antibody formation [26]. Additionally, morphine-pelleted mice demonstrated a decrease in B-cells and a decrease in the ratio of T-helper cells to T-suppressor cells, as shown by flow cytometric analysis [25]. Finally, implantation of a morphine pellet was associated with an increased lethality to bacterial infection with Listeria monocytogenes [24].

Potential Mechanism of Morphine's Immunosuppressant Actions

The battery of immunologic defects produced by morphine bears a striking resemblance to that observed in animals following chronic administration of glucocorticoids or chronic stress. Interestingly, the morphine pellet regimen we used in mice was also associated with adrenal hypertrophy [23] and an elevation of circulating corticosterone [27]; these observations prompted our investigations

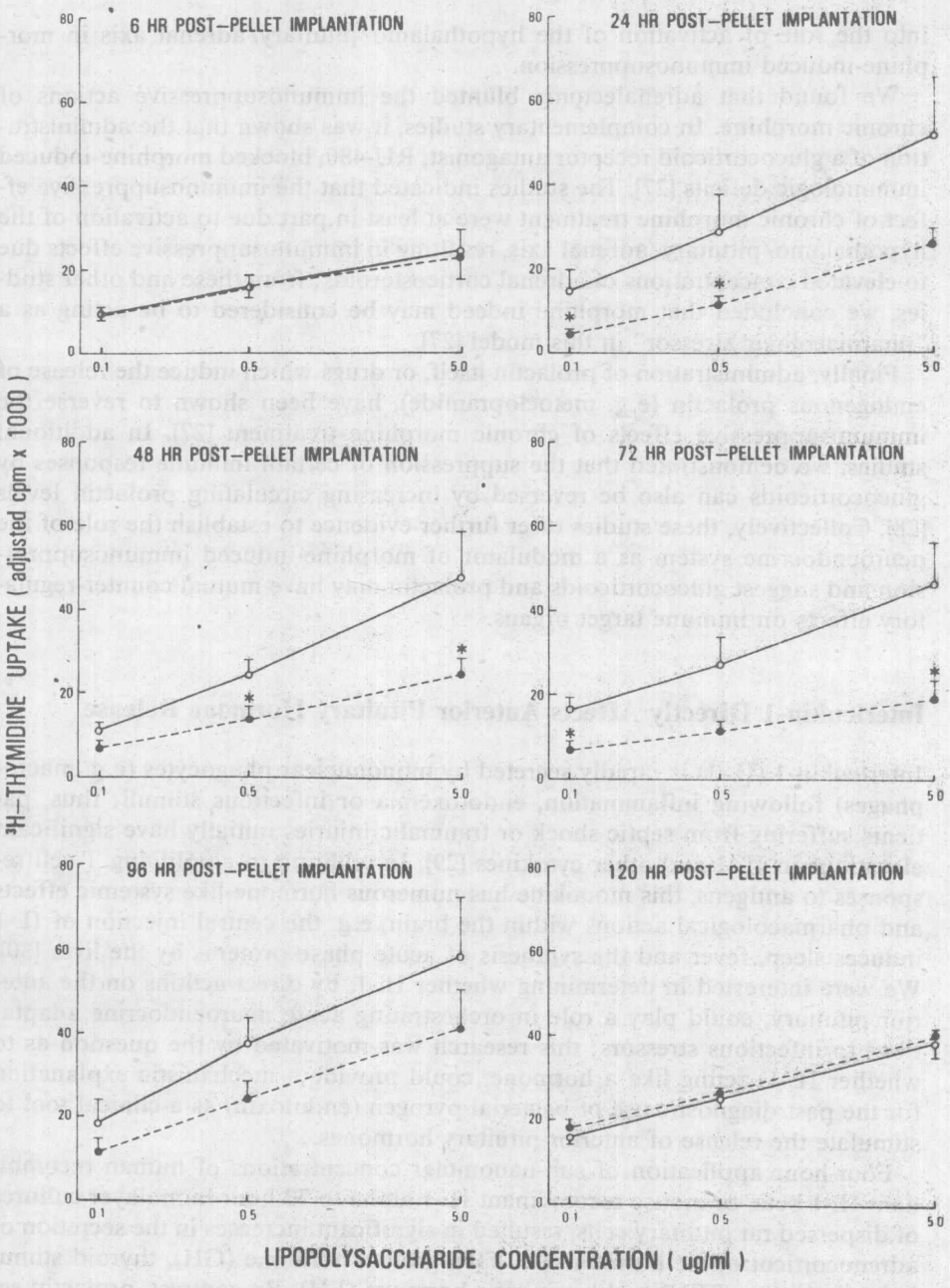

Fig. 2. Suppression of thymidine uptake stimulated by lipopolysaccharide in splenocytes obtained from placebo (open circles, solid line) or morphine-pelleted (closed circles, dashed line) mice at various times following initiation of chronic morphine exposure. See [18] for details

into the role of activation of the hypothalamo/pituitary/adrenal axis in morphine-induced immunosuppression.

We found that adrenalectomy blunted the immunosuppressive actions of chronic morphine. In complementary studies, it was shown that the administration of a glucocorticoid receptor antagonist, RU-486, blocked morphine-induced immunologic deficits [27]. The studies indicated that the immunosuppressive effect of chronic morphine treatment were at least in part due to activation of the hypothalamo/pituitary/adrenal axis, resulting in immunosuppressive effects due to elevated concentrations of adrenal corticosteroids; from these and other studies, we concluded that morphine indeed may be considered to be acting as a "pharmacologic stressor" in this model [27].

Finally, administration of prolactin itself, or drugs which induce the release of endogenous prolactin (e.g. metoclopramide), have been shown to reverse the immunosuppressive effects of chronic morphine treatment [27]. In additional studies, we demonstrated that the suppression of certain immune responses by glucocorticoids can also be reversed by increasing circulating prolactin levels [28]. Collectively, these studies offer further evidence to establish the role of the neuroendocrine system as a modulator of morphine-induced immunosuppression and suggest glucocorticoids and prolactin may have mutual counter-regulatory effects on immune target organs.

Interleukin-1 Directly Affects Anterior Pituitary Hormone Release

Interleukin-1 (IL-1) is rapidly secreted by mononuclear phagocytes (e.g. macrophages) following inflammation, endotoxemia or infectious stimuli; thus, patients suffering from septic shock or traumatic injuries initially have significant elevations in IL-1 and other cytokines [29]. In addition to amplifying T-cell responses to antigens, this monokine has numerous hormone-like systemic effects and pharmacological actions within the brain, e.g. the central injection of IL-1 induces sleep, fever and the synthesis of acute phase proteins by the liver [30]. We were interested in determining whether IL-1, by direct actions on the anterior pituitary, could play a role in orchestrating acute neuroendocrine adaptations to infectious stressors; this research was motivated by the question as to whether IL-1, acting like a hormone, could provide a mechanistic explanation for the past diagnostic use of bacterial pyrogen (endotoxin) as a clinical tool to stimulate the release of anterior pituitary hormones.

Four-hour application of sub-nanomolar concentrations of human recombinant IL-1 beta, or mouse recombinant IL-1 alpha to 72 hour monolayer cultures of dispersed rat pituitary cells, resulted in significant increases in the secretion of adrenocorticotrophic hormone (ACTH), growth hormone (GH), thyroid stimulating hormone (TSH) and luteinizing hormone (LH). By contrast, prolactin secretion was slightly decreased [31]. IL-1 also stimulated increased prostaglandin E2 production in these cultures; however, the cyclo-oxygenase inhibitor indomethacin (at doses that blocked PG-E2 secretion) when given along with IL-1 in the above system, did not affect the observed alterations in hormone release. The data suggest that, although IL-1 stimulates the arachidonic acid cascade, prosta-