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Review

Getting nervous about immunity

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ABSTRACT

Twenty-five years ago, immunologists and neuroscientists had little science of mutual interest. This is no longer the case. Neuroscientists now know that the first formally defined cytokine, IL-1, activates a discrete population of hypothalamic neurons. This interaction leads to the release of glucocorticoids from the adrenal gland, a hormone that has a long history in immunoregulation. Immunologists have been surprised to learn that lymphoid cells synthesize acetylcholine, the first formally recognized neurotransmitter. This neurotransmitter suppresses the synthesis of TNF. These discoveries blur the distinction of neuroscience and immunology as distinct disciplines. There are now 37 formally recognized cytokines and their receptors, and at least 60 classical neurotransmitters plus over 50 neuroactive peptides. These findings explain why both immunologists and neuroscientists are getting nervous about immunity and highlight a real need to apply integrative physiological approaches in biomedical research.

1. Introduction

Since the beginning of time, it has been known that animals and humans infected with pathogenic microorganisms become sick. Common symptoms are fever, anorexia, somnolence, psychataxia (inability to concentrate), fatigue, lethargy and pain. All of these are physiological responses that require activation of both the immune and nervous systems. It should therefore come as no surprise that the immune and nervous systems are inextricably linked in ways that dramatically affect our health and well-being.

Regulation of the major organs of the body has long been studied in the discipline of systemic physiology. Indeed, the first issue of the *American Journal of Physiology* was published in 1898. Seventeen years later, The *Journal of Immunology* appeared. As specific biomedical disciplines continued to develop, so did more specialized scientific journals. *Endocrinology* first appeared in 1927, and the *Journal of Neuroscience* was first published in 1981. During the past 50 years, many major biomedical journals have emphasized the publication of specialty rather that integrative papers. Immunologists, neuroscientists and psychiatrists were focused on their specific disciplines, even though common sense dictated that the brain and immune system must communicate with each other to ultimately change some type of behavior. Integrative physiology research that stressed communication and regulatory systems among major tissues and organs fell out of grace. With the more recent advent of open access journals, this trend toward growth of specialty journals continues.

It was in this historical context that the first issue of *Brain, Behavior and Immunity* appeared on March 1, 1987. Ader, Cohen and Felten wrote, "As a result, the neurosciences and immunology developed and matured without seriously considering the possibility that there might be channels of communication between these systems that could mutually influence their respective functions." and ". . ..the questionable conclusion that the immune system can, and therefore does, operate in an autonomous manner, *i.e.* independent of other physiological systems." [1]. Twenty-five years after these words were written, it has become abundantly clear that the immune and central nervous systems are not the sole captains of their own ship. They both regulate actions of the other. The immune system helps to maintain health by interacting in a coordinated fashion with many organ systems in the body, including the nervous system. As such, the immune system should be viewed as just another physiological system, like the cardiovascular, central nervous, renal, musculoskeletal and neuroendocrine systems [2]. All these physiological systems work together to maintain homeostasis and to promote proper body functioning in both health and disease. Integration of the immune system with all other bodily systems defines immunophysiology.

There is ample evidence to conclude that understanding the etiology as well as the treatment of many brain diseases requires

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a better understanding of immunology. Conversely, pathologies that target peripheral organs are affected by the nervous system. Neuroimmunology research has been classically focused on nervous system diseases such as multiple sclerosis, Parkinson's disease, Huntington's disease and Alzheimer's disease. But, solving and developing effective treatments for these nervous system pathologies requires more knowledge about functional links with the peripheral immune system. As but one example, recent evidence has established that major mental health disorders such as depression, schizophrenia, maniac depression and perhaps autism spectrum disorders are associated with abnormalities in the immune system, even though cause-and-effect relationships are not year clear [3]. Similarly, learning how the nervous and immune systems interact to affect pathologies outside the nervous system is also critical. For example, as discussed below, activation of the vagus nerve reduces tumor necrosis factor (TNFα) synthesis and improves survival during sepsis in animal models [4]. Type II diabetes, obesity, cardiovascular diseases and cancer and its treatments are major health issues of our times. Behavioral changes occur in all of these pathologies, and they can seriously affect quality of life of patients. Most diseases, regardless of whether the primary pathology affects a central or peripheral tissue, are associated with perturbations in communication systems between the immune and nervous systems of animals and humans alike. This link between medicine and physiology is probably one reason why Alfred Nobel did not name one of the five original prizes as the "Nobel Prize in Medicine." Instead, the name he chose that remains as one of his namesakes is the "Nobel Prize in Medicine or Physiology."

2. The physiology of immunology

Innate and acquired immunity are very important components of the physiology of the entire body, thus comprising the emerging area of immunophysiology. The flu viruses provide an excellent example of how the body and the brain work together to clear this infection. Influenza viruses generally gain access to the body *via* mucus membranes, such as those in the eyes and nose. Even though flu viruses normally persist outside the central nervous system, they induce symptoms that involve the brain within a couple days. The classic symptoms are fever, chills, headaches, somnolence and reduced appetite. The resulting malaise and fatigue reduce the motivation of flu patients to perform their normal activities. Although uncomfortable, these symptoms of sickness are generally considered to promote recovery and healing [5,6]. Most of these flu symptoms begin to subside after a couple days and disappear in seven to ten days.

The immune system engages its full armamentarium to remove influenza viruses from the body. Epitope-specific antibodies, CD8+ cytotoxic T cells and natural killer cells are the major effectors. But, various parts of the brain are responsible for regulating body temperature, appetite, sleep, pain and motivational aspects of fatigue. In order to determine if there are detectable changes that occur in the brain following viral infection, Jurgens et al. infected mice with a non-neurotropic strain of influenza [7]. By using very sensitive quantitative real time RT-PCR, no evidence of influenza virus could be detected in the hippocampus. Yet, dramatic changes occurred in the cytokine and neurotrophin mRNA profile of this brain structure: there was an increase in the proinflammatory cytokines interleukin (IL)-1β, tumor necrosis factor (TNF), IL-6 and interferon (IFN) α and a reduction in the expression of brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) (Fig. 1). These effects may be related to an increase in the number of activated microglia in the hippocampus, as detected by induction of ionized calcium binding adapter molecule 1 (Iba1) immunohistochemical staining. These

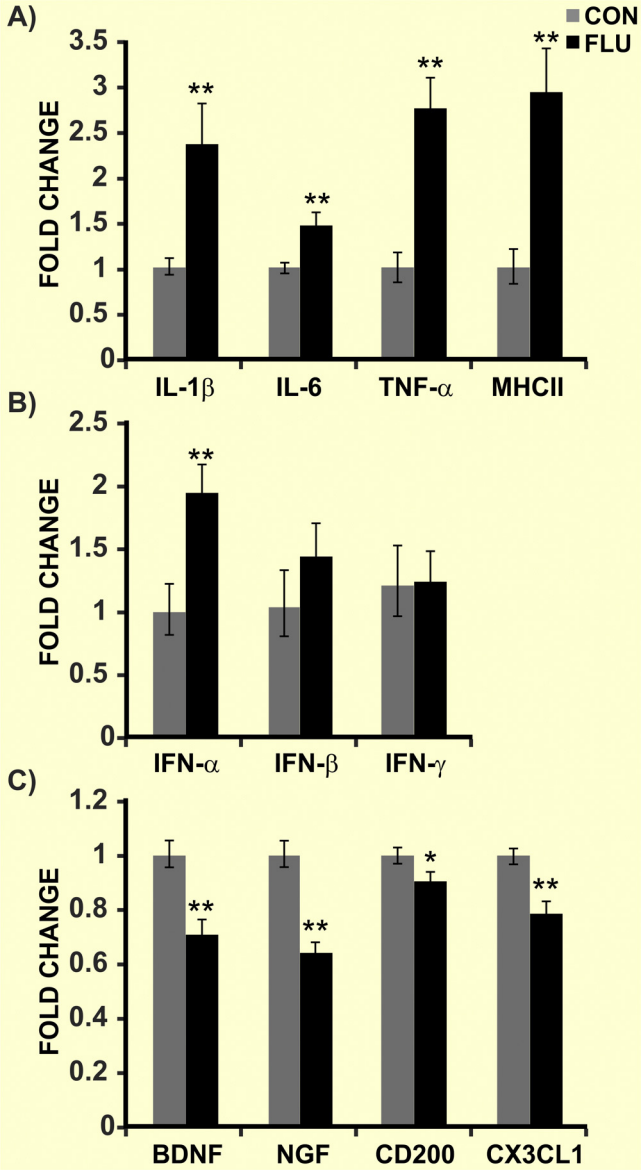

Fig. 1. A peripheral influenza infection regulates RNA expression of numerous cytokines in the brain. Although no virus could be detected in the brain, the influenza virus is able to induce an inflammatory response within the hippocampus. Reprinted with permission from [7].

data clearly establish that a viral infection in a peripheral organ like the lung causes changes in inflammatory proteins the brain. The resulting changes in behavior, which are cytokine mediated [8], help ensure survival.

The physiological circuits described above represent just another example of the benefits of organ systems working together for the benefit of the host. Cells of the immune system are not masters of their own fate. They are regulated by other physiological systems in the body, all of which serve to maintain homeostasis for the benefit of the host. It is not only antigens, but also nerves, hormones and local tissue factors that affect the multitude of activities expressed by lymphoid and myeloid cells, ranging from differentiation to recruitment by tissues to cytokine synthesis. But, an important question that remains is learning how the brain is informed that the body is infected with the flu virus. Several ideas have been proposed over the years, and these communication routes will be discussed below. However, recent advances in understanding immunological privilege of the brain are offering