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Neurological Mechanisms in Immune Regulation

Rodgers W[1*] and Tucker HO[2]

[1]Department of Biomedical Engineering, University of Texas at Austin, Austin, TX 78712, USA
[2]Department of Molecular Biosciences, The University of Texas at Austin, Neural Molecular Science, Austin, TX 78712-1191, USA

***Correspondig Author:** Rodgers W, Department of Biomedical Engineering, University of Texas at Austin, Austin, TX 78712 USA, Email: wyatt.abr@gmail.com

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Abstract

This paper is a survey of the neurological mechanisms involved in the regulation of immune function. Its specific focus is to explore the anatomical regions of the brain that mediate inflammatory responses throughout the body. It begins by briefly reviewing experiments that elucidate a connection between psychological process and immune function. It also introduces the physiological connections that enable communication between the central nervous system and peripheral immune system. It then examines the brain regions involved in regulating immune responses, with additional insights drawn from the principles of active inference in interoceptive processes.

Keywords: Psychoneuroimmunology; Inflammation; Autonomic nervous system; conditioning; Insula; interoception; Active inference; Bayesian

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Introduction

Immunity and Inflammation

The immune system's role is to protect an organism from damage and disease. Immunity is often viewed as being performed by a decentralized collection of cells referred to as the immune system. Whether it be damage or disease, the process by which the immune system responds to threat is referred to as inflammation. This process is performed by a complex system of soluble molecules, signalling pathways, and cells that allow the immune system to identify and respond to challenges. The nature of the response is dependent on the timing and context of signals that regulate critical checkpoints throughout the inflammatory process [1]. Highly-tuned regulation of this inflammatory response is essential to enable the body to respond appropriately to a huge diversity of threats. Classically the regulation of inflammation has been viewed as an independent and autonomous process of the immune system, however, we now know that this highly dynamic process is intimately integrated with the nervous system [2]. Integration between the immune and nervous systems extends immunity beyond a diffuse network of cells by incorporating the additional environmental information, processing power, and control mechanisms of the central nervous system. This enhances both

identification and response that ultimately enable the body to more efficiently and effectively respond to harm.

Immune Conditioning and Psychoneuroimmunology

The connection between the immune and nervous system was first realized in the mid-seventies from a seminal conditioning experiment by psychologist Robert Ader and immunologist Nicholas Cohen [3]. Using the immune suppressant cyclophosphamide, alongside a conditioning stimulus (CS), saccharin, they were able to evoke an immunosuppression in rats upon re-exposure to the CS alone. This observation demonstrated a functional link between behaviour and immunity and helped to establish a new field of scientific research subsequently dubbed "Psychoneuroimmunology". Since then, conditioning experiments have demonstrated both immunosuppression and stimulation in various animals, as well as humans [4]. This ability to modulate immune function based upon associated experience is referred to as the "learned immune response", and is becoming increasingly acknowledged as an evolutionarily acquired adaptive strategy, extending the concept of adaptive immunity beyond the classical definition [5].

Physiological Link

The nervous and immune systems are highly integrated at both the anatomical and molecular level, enabling central nervous system regulation of immune responses. These two systems interact through humoral, neuroendocrine, and direct neuroimmune modalities. Inflammatory signalling molecules known as cytokines can reach the brain through humoral interfaces at the blood brain barrier (BBB) [6] as well as through more permeable circumventricular organs [7]. Both neurons and resident immune cells located at these sites possess receptors to receive these inflammatory signals. Additionally, the CNS is able to modulate immune responses using neuroendocrine production of stress hormones through the hypothalamic-pituitary-adrenal axis (HPA axis) [8]. Most significantly, however, the CNS and immune system are directly integrated via the autonomic nervous system (ANS). Immuno-sensory signals are sent to the CNS via neurons on the afferent arm of the Vagus nerve, along with additional signals from somatosensory neurons from throughout the body [9]. These neurons possess receptors for detection of cytokines, infection, tissue damage, and pain [10,11]. Efferent signals from the CNS, through the Vagus and sympathetic nerve fibres, deliver acetylcholine and catecholamine mediated signalling (respectively) to immune organs that regulate inflammatory responses of immune cells [12] as well as elicit physiological changes that increase the body's ability to deal with threat. Afferent signals of the Vagus nerve induced by inflammatory molecules initiate efferent Vagal signals in a reflexive manner that result in anti-inflammatory effects [13], leading to the proposition of a neurological reflex response coined "the inflammatory reflex" [14]. Using the physiological interfaces described above, the CNS is able to assess immune status and modulate immune function to help protect the body.

Brain Function in Immunity

The brain's perception of internal processes is known as interoception. Interoception encompasses sensations critical to maintaining homeostasis such as heart-rate, blood-pressure, hunger, and immune status. Using both the humoral and visceral nervous system connections described above, the CNS integrates these immune signals across various regions of the brain in order to regulate inflammation [15].

Brain Anatomy

Afferent immune signals from the Vagus nerve are received in the brainstem by the nucleus tractus solitarius (NTS), shown by enhanced metabolic function in the NTS after

intraperitoneal (IP) lipopolysaccharide (LPS) exposure in mice [16]. These signals are also received by and projected into additional brain structures such as the rostral ventrolateral medulla (RVLM), parabrachial nucleus (PB), ventrolateral medulla (VM), both the paraventricular (PVN) and supraoptic nuclei (SON) regions of the hypothalamus (HT), the amygdala (Am), thalamus (Th), and ultimately to the cortical regions of the anterior insular cortex (AIC) and anterior cingulate cortex (ACC). [2, 15, 17]. Immune activation of resident immune and neuronal cells via the humoral pathways described above first interact with the hypothalamus and then to the amygdala and cortical regions where they then interact with the motor response paths in the same fashion as the visceral signals above [16]. Efferent neuroimmune modulating signals are generated in the dorsal motor nucleus (DMN) and RVLM for Vagal and sympathetic pathways respectively.

Brain Activity in Immune Interoception & Conditioning

Imaging, specific lesions, and metabolic mapping have been used to identify the brain regions involved in immune regulation and conditioning. The anterior insular cortex (AIC) plays a significant role in both response and conditioning of immune phenomena. fMRI imaging in humans shows increased activity in the AIC within 2-3 hours of mild immune challenges with LPS or Typhoid vaccine [18, 19]. Specific lesions to the AIC in mouse models demonstrate that the AIC is required for both the acquisition and evocation of immunosuppression conditioning [20, 21]. Metabolic monitoring also shows increased c-Fos production (a protein marker for neuronal activity) [22] in the AIC during the evocation of a conditioned increase in antibody production [23]. Similar to the AIC, the thalamus shows increased blood flow and metabolic activity during mild immune challenge as well [18,19]. The amygdala also plays a critical role in immune interoception. The amygdala is required for acquisition of conditioned immune suppression and additionally has been shown to have increased metabolic activity and cytokine production during IP LPS challenge in mice [21, 24]. Inversely, the hypothalamus is not required for the acquisition of conditioned immune suppression, but is required its evocation [21] Continued research into the brain regions involved in immune regulation will be required to fully understand these regulatory pathways. The concept of an “immunological homunculus” has been proposed as an immune analogue to the cortical homunculus, as it would map the regions of the CNS associated with immune functions [25].

Active Inference in Neuroimmune Regulation

The application of Bayesian active inference as a theoretical framework for understanding interoceptive processes offers further insights into the brain regions involved in immunity. In this framework, the brain’s goal is to minimize the ‘surprise’ associated with interoceptive sensations. It does so by creating predictive models that filter, attenuate, and compare sensations to prior experiences in order to more efficiently maintain homeostasis [26]. The formation of these predictive models provides a possible explanation for the psychoneuroimmunology conditioning phenomena discussed previously. Anatomically, the AIC is likely the key structure that generates, compares and updates these interoceptive predictions [27]. This assumption aligns with previously mentioned studies demonstrating the requirement of the AIC in acquisition and evocation of immune conditioning. Better understanding of active inference in interoception may increase our understanding of the anatomical regions of the brain involved in neuroimmune regulation.

Conclusion

Our view of inflammation regulation has evolved thanks to illuminating studies that have demonstrated the critical role of the nervous

system in this process. Exploration of psychoneuroimmunological phenomena, neuro-immune physiology, and CNS regulation of immunity will continue to help clarify the mechanisms by which the body integrates two of its most complex systems in order to best protect it.

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