endocrines

Perspective

Insulin Resistance and Glucose Metabolism during Infection

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Abstract: Specific critical functions of endocrine and immune cells ensure that an individual remains healthy and free from infection. This study aimed to explore immune–endocrine associations involved in disease. **Methods:** The PsycINFO, PubMed, Web of Science, and CINAHL databases were searched for relevant articles using the following search terms and phrases: "hormones", "hormonal responses", "immune system", "endocrine system", "infection", "immune cells", "endocrine cells", "infection", "immune", "endocrine", and "interactions". The search was limited to articles published between 2009 and 2023. **Results: A review of ninety-three studies** showed that metabolic activity levels in the body as well as energy consumption patterns are affected by feedback loops that connect the endocrine and immune systems. The associations between endocrine cells and immune cells are complex and involve a wide range of hormones, molecules, and receptors related to antipathogen responses and metabolic regulation. **Conclusions:** During infection, endocrine cells and immune cells interact via feedback loops to ensure optimal energy utilization and a timely response to pathogens. Therefore, the endocrine system helps to regulate systemic metabolism while controlling the outcomes of regulatory elements of the immune system.

Keywords: infection; endocrine system; crosstalk; hormones

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1. Introduction

Cells within the human body carry out specialized functions to promote health [1]. In addition, specialized cells ensure that the metabolic requirements of other cells are always met [1]. In humans, this process entails maintaining the homeostasis of electrolytes, gases, and nutrients [2,3], in which the endocrine system plays a critical role. The endocrine system is a chemical messenger system that consists of receptors and feedback loops mediated by hormones released from different glands into the circulatory system to regulate a target organ [4–6].

In humans, the endocrine system comprises a network of cells that communicate with other cells to ensure that certain factors, such as nutrient concentrations at the organ level, are carefully maintained and managed [7,8]. Before an endocrine response is initiated through hormones, homeostatic imbalance is detected by receptors on sensory cells [1]. The organs responsible for regulating imbalanced parameters are stimulated by signaling pathways and hormones to initiate responses to restore homeostasis. In recent years, it has been reported that interactions between the endocrine and immune systems are critical for maintaining homeostasis [1,9–11]. Immune cell function is highly dependent on the availability of glucose for metabolism [1,12,13]. Based on these findings, researchers have explored the interactions between the immune and endocrine systems, especially in the context of metabolic diseases [14–16]. The primary aim of this study was to examine immune–endocrine interactions and to assess the physiological processes underlying these interactions.

2. Methods

The current study examined immune–endocrine interactions by reviewing the existing body of research. The results of relevant studies in the PsycINFO, PubMed, Web of Science, and CINAHL databases were analyzed. Articles potentially related to the research topic were identified using the following search terms and phrases: "hormones", "hormonal responses", "endocrine system", "infection", "immune cells", "immune system", "endocrine cells", "infection", "immune", "endocrine", and "interactions". The search was limited to articles published in the four electronic databases between 2009 and 2023. The abstracts of the available studies were carefully reviewed to evaluate their quality and appropriateness, and selected articles were used to investigate the interactions between immune cells and endocrine cells during infection. The algorithm of studies included into the review is shown in Figure 1.

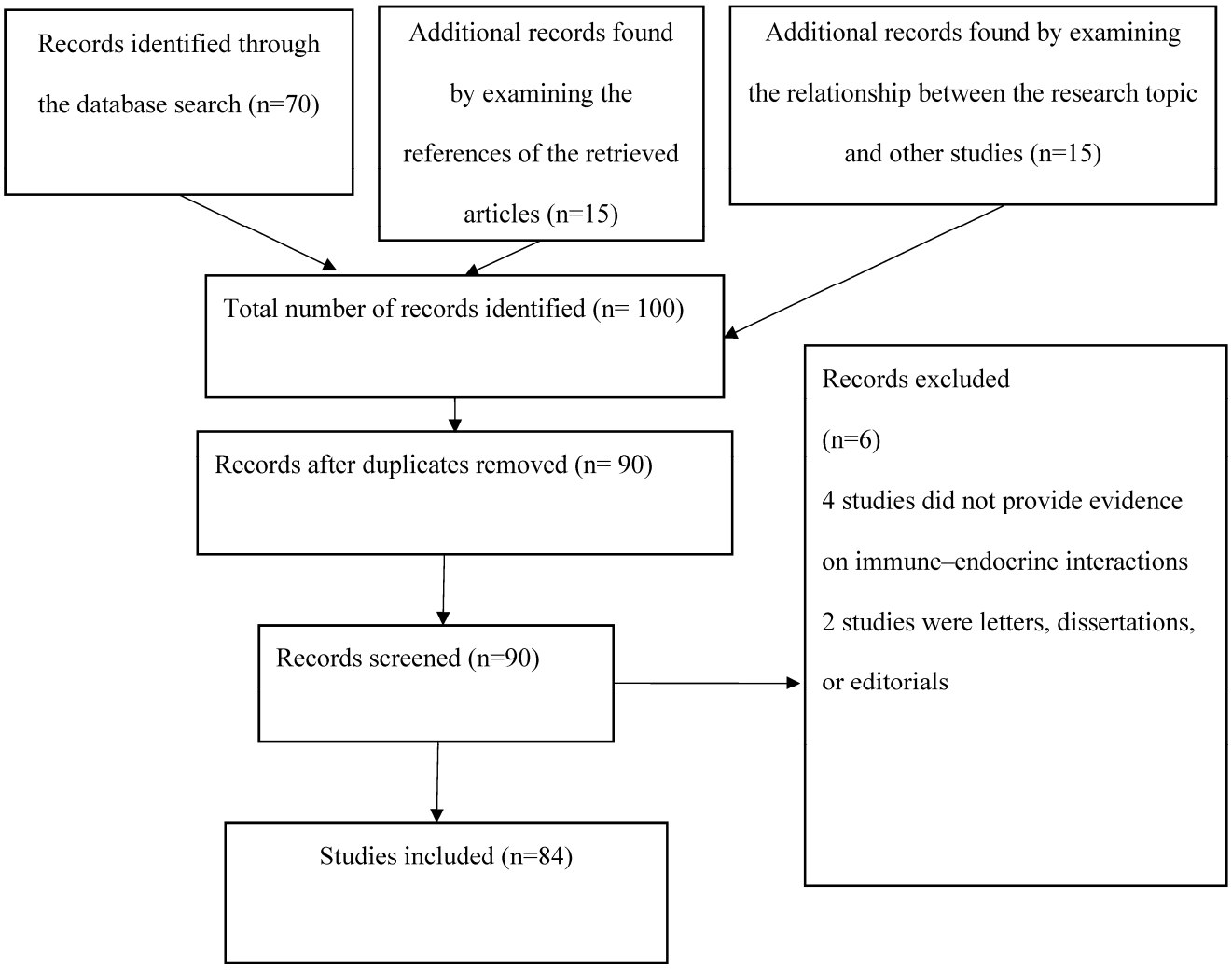

Figure 1. PRISMA flow diagram.

2.1. Endocrine System and Immunity

Webber et al. provided essential information on how the endocrine system influences human immunity in the context of lung diseases [17]. This study indicated that the impairment of the endocrine response in the lungs significantly impacts the balance between anti- and pro-inflammatory immune responses. Therefore, endocrine cells play an essential role in fostering immunity against lung infection [17].

Related to this research by Webber et al. [17], there is research on the role of peroxisome proliferator-activated receptor gamma (PPARy) in high-risk infections associated with

chronic metabolic diseases (CMDs). Silva et al. reported that PPARy activation regulates host cell activities, hence controlling inflammation in CMDs. In essence, PPARy agonists exhibit pro-resolutive and anti-inflammatory properties that increase the ability of host cells to fight pathogens. These agonists also facilitate improved control of hormone production and enhance the capacity to restore lipid and glucose homeostasis in the body [18].

Bansal et al. reported essential information regarding the association between the endocrine system and the immune system [19], affirming that people with metabolic syndrome are at risk of poor disease outcomes and might experience symptoms of severe coronavirus disease (COVID-19) [19]. Furthermore, individuals with metabolic syndrome have a pro-inflammatory environment that contributes to the dysregulation of the host immune response to COVID-19. According to Bansal et al., this dysregulation also promotes hyperinflammation, poor immune responses, thrombosis, and microvascular dysfunction [19].

Additionally, Muthusami et al. suggested that endocrine system glands play an essential role in influencing immune cell proliferation and differentiation, as well as the memory characteristics of the immune system [20]. This prior study identified high interdependence between the endocrine and immune systems and determined that disturbance in their crosstalk leads to poor immunity and increased susceptibility to disease [20]. Wensveen et al. reported essential information on the role of immune–endocrine interactions in protecting against disease [21]. In general, the immune system requires optimal access to nutrients to enable the body to respond to antigens. Furthermore, the endocrine system activates the secretion of these nutrients, highlighting the strong interdependence of the two systems [21].

Rowe et al. provided crucial information on how immune–endocrine interactions affect sleep disorders [22]. In particular, this study revealed that immune–endocrine interactions play an essential role in both healthy sleep and pathological sleep caused by immunological stressors or brain injury [22]. Another study [23] closely related to this study revealed the importance of crosstalk between the immune and endocrine systems in maintaining good health. Specifically, the authors determined that the disruption of the endocrine system affects the gonadal axis and the hypothalamic–pituitary–adrenal (HPA) axis, resulting in altered hormonal communication between the immune and nervous systems, thereby rendering the body vulnerable to disease [23]. Moreover, Zefferino et al. revealed a linear relationship between the endocrine and immune systems involved in protecting the human body from disease [24]. In particular, this study affirmed that stress affects endocrine secretions, leading to a lack of essential nutrients required by the immune system to establish immunity against pathogens [24].

Another study [25] provided essential information for the current review because it provides insight into the importance of the interrelationship between the endocrine and immune systems. Specifically, this study showed that the impairment of immune cell regulation and defects in innate immunity led to organ-level atrophy and endocrine system dysfunction; these changes affect insulin secretion, increasing the risk of type 1 diabetes [25]. In addition, another study [26] confirmed that a compromised immune system increases susceptibility to various pathogens.

De Luca et al. provided crucial information on the importance of the endocrine system in influencing the activities of the immune system [27]. This study found that thyroid hormones (THs) help immune cells establish necessary immunity in humans and are needed for a proper immune system feedback response in various circumstances [27]. In people who are susceptible to autoimmune disorders, the destruction of endocrine–immune interactions leads to autoimmune thyroid dysfunction [28]. As thyroid glands are the target of autoimmune diseases, it is essential to ensure optimum interactions between the endocrine and immune systems [29]. A systematic review by Montesinos et al. revealed that the interplay between the endocrine and immune systems plays a critical role in ensuring thyroid function and adaptive immunity [30]. Therefore, endocrine disruption impairs the normal functioning of the endocrine system, leading to a lack of the

essential secreted molecules needed by the immune system to establish immunity against pathogens [28].

2.2. Differences in Immune–Endocrine Interactions during Viral, Bacterial, and Fungal Infections

Endocrine–immune interactions during bacterial, viral, and fungal infections are similar. In particular, infections with any of these three types of pathogens can activate the sympathetic nervous system (SNS) and the HPA axis, leading to the production of stress hormones, including ACTH and CRH. These hormones have anti- and pro-inflammatory effects and thus influence immune system activity [22,23].

The increase in the HPA axis with the result of increased cortisol production is particularly pronounced in viral diseases. The corticosteroids are primarily immunosuppressive. The release of cortisol regulates the immune response and counteracts an excessively increased immune response. The immune reaction is slowed down by cortisol [22,23].

In contrast, bacterial infections often lead to an increase in thyroid hormone production [30]. Thyroid hormones increase the immune system response [30,31]. Above all, they have an immune-stimulating effect [30,31]. In bacterial infections, neutrophils are stimulated and attracted more than any other cell type.

In contrast, fungal infections primarily lead to IgE production and the formation of eosinophils. Due to the high IgE production and eosinophilia, this can lead to the development of allergies [32].

In viral infections, the immune system is stimulated through interferon-gamma, and T lymphocytes are primarily stimulated [33,34].

3. Results

This study entailed a systematic review of published articles reporting animal model studies, clinical trials, cohort studies, and experimental studies as well as reviews. The literature was carefully examined, summarized, and interpreted to elucidate the association between immune cells and endocrine cells. Research indicates a correlation between the endocrine system and the immune system [16]. The immune system is directly involved in protecting organisms from pathogens, and the endocrine system regulates systematic homeostasis [1]. Immune–endocrine crosstalk is vital for immune responses because it coordinates bodily functions to allow for appropriate responses to adverse events and stress [18,33]. The endocrine system increases energy levels in immune cells to facilitate healing in the presence of infection. In the absence of infection, immune cell metabolism usually switches to energy-intensive anabolic metabolism after activation [1,33].

Additionally, some immune cells, such as T cells, rely on glycolysis to generate ATP and other molecules needed for biosynthetic pathways [34]. These processes are necessary to generate energy to protect against lethal pathogen infection. Once the pathogen has been eliminated, the redundant immune cells die via apoptosis, and the metabolism of the remaining cells reverts to less energy-intensive catabolic metabolism to support normal activity [35–37]. Immune cells play a key role in maintaining homeostasis by guiding the endocrine system's response to a wide range of stimuli, including metabolic stress and infection [35]. In recent years, research has identified a clear interaction between the immune and endocrine systems during the development of complex diseases and infections [38–41] and in some mild psychiatric diseases [42]. Furthermore, research shows that immune cells influence the response mediated by the endocrine system during infection [43,44]. Thus, there appears to be important bidirectional communication between these systems that helps to maintain normal homeostasis and support the fight against pathogens.

The body is seriously challenged during infection. First, host immune cells may increase intracellular metabolism to respond to invading pathogens. The optimal functioning of innate defense mechanisms may be influenced by different factors, including sufficient energy availability [45]. Second, there is a need to restrict nutrient availability to pathogens to effectively manage the infection [46,47], and studies have revealed that different pro-inflammatory cytokines, such as TNF and IFN-γ, can increase insulin resistance in patients

with obesity-linked systemic inflammation [47]. In addition, researchers have reported that infection can lead to the loss of glycemic control, resulting in hypo- or hyperglycemia. Importantly, infection-causing pathogens can induce insulin resistance in humans without changing postprandial blood glucose levels [1].

More recently, immune-mediated metabolic regulation has been reported to help restrict pathogen access to nutrients while facilitating the optimal function of immune cells. Accordingly, there is a need to maintain the balance between providing sufficient energy for immune cells and ensuring that pathogens do not gain access to nutrients during infection. This balance has been previously studied in the context of different infections in humans to determine the role of immune–endocrine interactions.

3.1. Euglycemic Hyperinsulinemia

During mild infections, some patients develop cytokine-induced insulin resistance, even in the absence of changes in blood glucose levels [1]. For instance, people infected with human immunodeficiency virus (HIV) tend to have high insulin levels, but their fasting plasma glucose levels are similar to those of their healthy counterparts [47]. Similarly, researchers have found that people who have an acute mild respiratory infection show increased insulin levels, but their blood glucose levels are unchanged at the time of diagnosis [1,48]. Experiments in animal models have revealed that cytomegalovirus (CMV), mild influenza, and lymphocytic choriomeningitis virus (LCMV) infections can induce insulin resistance without the loss of glycemic control [48]. Furthermore, increased pancreatic insulin output can compensate for infection-induced insulin resistance, which helps to prevent postprandial hyperglycemia [48]. Altogether, these findings show that increased blood glucose levels cannot be considered the cause of infection-linked insulin resistance. Instead, researchers have proposed that inflammatory mediators induce insulin resistance to redirect nutrients, such as glucose, away from the muscles and liver to immune cells [1].

Notably, insulin resistance does not automatically result in the increased availability of systemic nutrients. During fasting, glucose uptake is often mediated by insulin-based mechanisms [49,50]. Organs that are highly dependent on glucose, such as the brain and immune system, express glucose transporters that acquire glucose from the blood, even when blood glucose levels are low [1,50,51]. Thus, postprandial insulin production is perhaps associated with the need to inhibit hyperglycemia-induced tissue damage rather than to regulate resource allocation.

The primary role of infection-induced insulin resistance appears to be related to compensatory hyperinsulinemia. Insulin is considered a signal of acute nutrient availability and an indication that organs need to change their energy sources and rely more on anabolic metabolism [52]. The intracellular components engaged in insulin signaling are the same as those associated with the endocrine system. For example, the signaling pathway mediated by the costimulatory molecule CD28, found in T cells, converges with the pathway mediated by insulin receptors via PI3K to facilitate signaling [52–54]. Both insulin receptor activation and CD28 stimulation lead to increased glucose transporter expression. Furthermore, these changes can induce anabolic metabolism [55,56].

During infection, IFN-γ can promote insulin insensitivity by downregulating insulin receptor expression, which may cause reactive hyperinsulinemia [57]. However, the ablation of IFN-γ receptors on myocytes prevents systemic insulin resistance, thus reducing the risk of reactive hyperinsulinemia in muscles [1,58]. These results further support the argument that euglycemic changes are not the primary goal of immune-mediated biological alterations [59,60]. Currently, it is not clear why the increase in systemic insulin levels does not cause a reduction in fasting plasma glucose levels. However, it is argued that these observations may relate to the compensatory response by pancreatic α-cells to increase glucagon production [59,60]. From these studies, it can be concluded that infection-linked insulin resistance may be the outcome of increased systemic insulin levels and pro-anabolic changes in the body during infection [1].

3.2. Anorexia, Infection, and Blood Glucose Levels

Anorexia is another condition related to infection in which interactions between endocrine and immune cells have been explored. When the body is attacked by pathogens, the immune system releases cytokines, such as IL-6, TNF, and IL-1β [1], which promote the release of leptin from adipocytes. In some cases, cytokine production induces nausea and vomiting to reduce food intake [61]. Research shows that infection-induced anorexia might not cause hypoglycemia, as is the case with prolonged fasting [21]. During fasting, nutrients in adipose tissue and the liver are converted to glucose via glycogenolysis and hepatic gluconeogenesis [21]. Therefore, the key effect of anorexia within the context of endocrine–immune system interactions is the influence on the metabolic state.

The immune system does not typically hinder anabolic metabolism once the pathogen is eliminated. Under homeostatic conditions, immune cells are subjected to endocrine control via hormones such as adiponectin to limit nutrient use [50]. Under such conditions, infection is an acute threat to the body, and cytokines are released to help restore normal function. Furthermore, pathogen entry leads to the upregulation of costimulatory molecules and the release of immune cells from normal endocrine-linked control. For example, an infection that leads to anorexia can prompt the release of CD28 ligands from dendritic cells and the subsequent increase in expression of the glucose transporter GLUT1 by T cells. These changes enable optimal T-cell activity, even when glucose levels are below 0.5 mmol/L [55,56].

In these contexts, immune cells can operate with maximum efficiency, while the body struggles in a state of nutrient preservation after a period of starvation. Other studies have shown that immune cells might benefit from the infection-induced fasting state [62–64]; for example, in this state, CD8 T-cell function increases following the conversion of acetate to acetyl-CoA [1,65]. Although infection-induced anorexia may not always lead to the formation of CD8 T cells, it increases the concentration of circulating ketone bodies.

3.3. Stress Hyperglycemia and Infections

Some infections and conditions, such as sepsis and physical trauma, cause severe disease. In such cases, the individual experiences a considerable increase in blood glucose levels, leading to stress hyperglycemia [66]. Severe stress triggers a systemic neuroendocrine response characterized by the release of different hormones, such as cortisol, norepinephrine, and epinephrine. These hormones usually promote gluconeogenesis in the liver [1] and function with other immune system molecules, such as IL-1β, TNF, and IL6, to promote insulin resistance in hepatocytes [67,68].

Initially, researchers argued that stress hyperglycemia might have adverse effects on patient health and well-being. However, recent investigations have revealed higher mortality rates among hyperglycemic patients subjected to intensive blood sugar regulation in the ICU than among controls [69]. Furthermore, hyperglycemia often arises to ensure sufficient glucose supply to critical organs, even in the context of reduced blood flow. An example is a patient who develops septic shock as a result of an infection [69]. The increase in glucose levels protects organs from negative pathological effects, such as hypoxia. However, a prolonged state of hyperglycemia causes apoptosis and induces metabolic complications such as diabetes mellitus [1]. The above results demonstrate that, although infection tends to cause substantial changes in the regulation of metabolic processes by the endocrine system, alterations linked to systemic glycemia are not common [1,70,71]. Additionally, such glycemic changes might occur only when a patient has a severe infection or when the body cannot use a less detrimental mechanism to eliminate a pathogen.

3.4. Diabetes and Infections

The biological changes in people with type 2 diabetes mellitus have provided further evidence for the presence of interactions between immune cells and endocrine cells [72–75]. Type 2 diabetes mellitus is characterized by the inability to maintain postprandial or fasting blood glucose levels below a standard value. Individuals diagnosed with this disease may also have other severe conditions, such as stroke, renal failure, and heart failure [72,76–78]. Available data show that infection can increase the risk of diabetes, especially in people with metabolic dysfunction [79–82].

Moreover, type 2 diabetes mellitus tends to predispose individuals to infection because it interferes with insulin sensitivity [68–71]. Recent investigations have revealed that infections tend to target signaling cascades involving the activation of AKT and protein phosphatase 2A (PP2A), negatively impacting insulin sensitivity [72–74]. Therefore, molecular evidence suggests a possible causal relationship between infection and diabetes, thus highlighting the interaction between immune cells and endocrine cells [1,83].

4. Discussion

The association between endocrine cells and immune cells has been studied extensively. Available research shows that immune cell function is influenced by the presence or absence of inflammatory cells. Interestingly, the immune system consumes approximately 20% of the energy in the body, with this percentage increasing to approximately 30% in a person with an infection [11,12].

When a pathogen enters the body, different immune cells, such as T cells, proliferate to rapidly increase their numbers. Furthermore, other immune cells, such as macrophages and natural killer (NK) cells, transition from performing efficient oxidative phosphorylation to more nutrient-intensive glycolytic metabolism to generate the energy required to combat pathogens [13]. The rapid changes that occur in the body are usually influenced by cytokines and receptors that act as immunological hormones. Together, the findings regarding these processes indicate that the immune system tends to operate independently of the endocrine system [14].

Wensveen et al. noted that metabolic regulation in immune cells independent of the endocrine system makes sense only if the rapid response to pathogens is prioritized over energy efficiency [1]; furthermore, the authors stated that evidence supports the intertwining of processes within the endocrine and immune systems during infection. For instance, adipose tissue, which usually communicates nutrient levels in the body, is capable of inhibiting or promoting the responsiveness of immune cells to stimuli [15,16]. Additional evidence suggests that cytokines influence factors such as body temperature and glucose uptake that are largely controlled by endocrine hormones [16,32]. Immune cells have also been reported to effectively respond to other hormones, such as insulin, that regulate systemic metabolism [33].

The current review shows that the immune and endocrine systems usually control unique processes in multicellular organisms. Initially, their functions may seem to be independent, as it is widely reported that the endocrine system is involved in regulating systematic homeostasis and that immune cells offer protection against pathogens. Nevertheless, research suggests that extensive feedback loops facilitate the interactions between these two systems and coordinate optimal responses to infection [1,70,72]. These interactions may be elucidated by examining how each system disrupts existing feedback loops during an infection. However, the complex molecular bases of these processes make it difficult to clearly delineate the actual mechanisms involved.

5. Conclusions

Interactions between the endocrine and immune systems have attracted the attention of researchers. The present study shows that cell populations, receptors, and molecules in each system affect the feedback loops involved in the host response to infection. The endocrine system helps to regulate systemic metabolism while controlling the effect of

regulatory elements within the immune system. Further studies are needed to explore the molecular basis of the responses of these two systems to infection. In addition, it is imperative to conduct further studies to determine the extent to which the endocrine system affects how immune cells combat pathogens.

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