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Virus-mediated modulation of the host endocrine signaling systems: clinical implications

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Viruses, which are among the simplest infective pathogens, can produce characteristic endocrine manifestations in infected patients. In addition to the classic modification of the host endocrine system by either direct or indirect destruction of the endocrine organs and/or effects exerted by systemic production of inflammatory and/or stress mediators, recent progress in molecular virology and endocrinology has revealed that virus-encoded molecules might alter the host endocrine-signaling systems by affecting extracellular and/or intracellular signal transduction and hormone sensitivity of host target tissues. Here, we provide a brief overview of such viral-mediated modulation of host endocrine signaling systems. We propose that virus-encoded molecules and the signaling systems they influence are potential therapeutic targets for the treatment of disorders that are associated with some viral infections.

Introduction

Viruses are among the simplest infective pathogens on earth. Viruses cause a variety of pathological conditions of occasionally pandemic proportions, and constitute potential major threats to the human population [1]. Even after the development of vaccines, which have been tremendously effective in controlling many viral infections, viruses are still among the most common human pathogens, sometimes causing life-threatening diseases [1]. The latter is evident from recent epidemics, such as acquired immunodeficiency syndrome (AIDS), caused by the human immunodeficiency virus type-1 (HIV-1), and severe acute respiratory syndrome (SARS), caused by the SARS corona virus [2,3].

Replication and survival of viruses inside host cells are dependent on the cellular machinery of the host. Viruses might usurp the regulation of and change host-cell functions for their benefit. Indeed, through molecules encoded by viral genetic material, whose expression is synchronized with specific phases of the viral life cycle, viruses increase the chance of their own replication and survival. Virus-induced alterations of host-cell functions cause a broad spectrum of cellular damage, from a transient, mild change of function to neoplastic transformation, apoptosis and necrosis. Recent research has revealed that viruses, through the molecules they encode, modulate endocrine signaling systems in the host to cause characteristic changes in both endocrine organs and hormone target tissues.

Here, we provide a brief overview of recent progress in understanding virus-induced modifications of endocrine signaling systems and of the resultant pathological states in the host. On the basis of this understanding, potential new therapeutic targets for the development of anti-viral disease agents are envisioned.

Virus-induced modifications of host endocrine systems: the classic view

Generally, entry of viruses into and infection of host tissues evokes several levels of host reactions that might be associated with pathological manifestations. Thus, infection of host tissues might damage infected organs and tissues directly. By contrast, viruses themselves and tissues that are infected with viruses might activate the host immune reaction, leading to the development of inflammatory lesions and/or the destruction of infected tissues [4]. In addition, host immune responses induced against viruses and infected tissues might damage uninfected tissues, partly because of the similarity between viral antigens and those of host cells (molecular mimicry), and because of a systemic, generalized inflammatory reaction that results in dysfunction of multiple organs [5].

Viral-induced inflammation and viremia also activate the systemic stress response, in which the hypothalamic–pituitary–adrenal (HPA) axis has a major role. Secreted glucocorticoids, the end-effectors of the HPA axis, protect peripheral organs from inflammation-induced tissue damage by suppressing an overshoot of the host immune reaction and by rendering tissues resistant to toxic inflammatory agents [6–8]. Thus, viral infections classically induce the host reactions shown in Box 1 and Figure 1. Examples of classic host responses to viral infections are also described in Table 1.

Modification of host endocrine signaling systems by virus-encoded molecules: new mechanisms

Recent accumulation of knowledge about eukaryotic and viral genes has expanded our understanding of the roles of

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Box 1. Virus-induced alterations of the host endocrine system

- Activation of the HPA axis/stress system indirectly, as a result of a general inflammatory response to the systemic viral infection and secretion of mediators of inflammation with stress system-stimulating activity.
- Damage of virus-infected endocrine cells by viral replication, proliferation and assembly.
- Damage of virus-infected endocrine organs by activation of the immune reaction against these organs.
- Damage against uninfected endocrine organs through an autoimmune mechanism.
- Alteration of hormonal activity and/or hormone secretion by viral gene products.

both host- and virus-encoded molecules in the regulation of gene expression and function. Numerous cell-surface molecules and nuclear hormone receptors (NRs) that transduce the signals of circulating hormones in the cytoplasm and/or the nucleus have been identified and their biological functions have been elucidated. In parallel, it has become evident that some viruses cause pathological changes because they encode molecules that affect host signaling pathways directly [9,10] and these actions sometimes cause serious clinical problems (Table 2) [10,11]. Indeed, viruses have developed some of their unique, highly sophisticated molecules through the mutational selection of protein isoforms that increase the chance of their replication and/or survival inside infected cells, and their propagation from cell-to-cell and host-to-host.

These viral molecules regularly influence crucial steps in host signaling systems and, thus, dramatically change cellular functions towards conditions that are beneficial to the replication, survival and/or propagation of the viruses that encode them. Sometimes, these viral molecules mimic functions of host proteins. For example, HIV-1-encoded gp120 molecules, which are located on the surface of the viral particle and have a major role in the entry of viruses into target cells, demonstrate amino acid sequence similarity to the growth hormone-releasing hormone (GHRH) receptor of the host and suppress the activation of this receptor by GHRH. This phenomenon might contribute to growth retardation of HIV-1-infected children [12]. This viral molecule is also similar to vasoactive intestinal peptide, which interacts with CD4, a receptor for HIV-1, to facilitate its entry into T cells [13,14]. The amino acid sequence of the HIV-1 Nef protein resembles a portion of the thyroid-stimulating hormone receptor, and this cross-reactivity might contribute to the development of Grave's disease in HIV-1-infected patients [15].

In addition to their extracellular actions, many viral molecules act inside infected cells to modulate intracellular host signaling systems, including transcriptional regulation of target genes by hormones. These molecules are intended primarily to benefit viral replication, but, frequently, they alter the intracellular milieu, disturbing cellular functions as a 'side-effect' and causing specific, recognizable, pathological conditions [10,16]. In the following sections, examples of extracellular and intracellular modifications of host endocrine signaling systems caused by viral molecules are discussed.

PTH-related polypeptide (PTHrP)-mediated hypercalcemia and the human T-cell leukemia (lymphotrophic) virus type-1 (HTLV-1)

Human T-cell leukemia (lymphotrophic) virus type 1 (HTLV-1), the single-stranded RNA virus of the *Retroviridae* family that specifically infects CD4-positive T cells, is a causative agent of adult T-cell leukemia (ATL) and HTLV-associated myelopathy [11]. ATL patients infected with HTLV-1 may also develop hypercalcemia because of aberrant expression of parathyroid hormone (PTH)-related protein (PTHrP) [17]. PTHrP is a 141 amino acid protein that shares significant N-terminal sequence homology

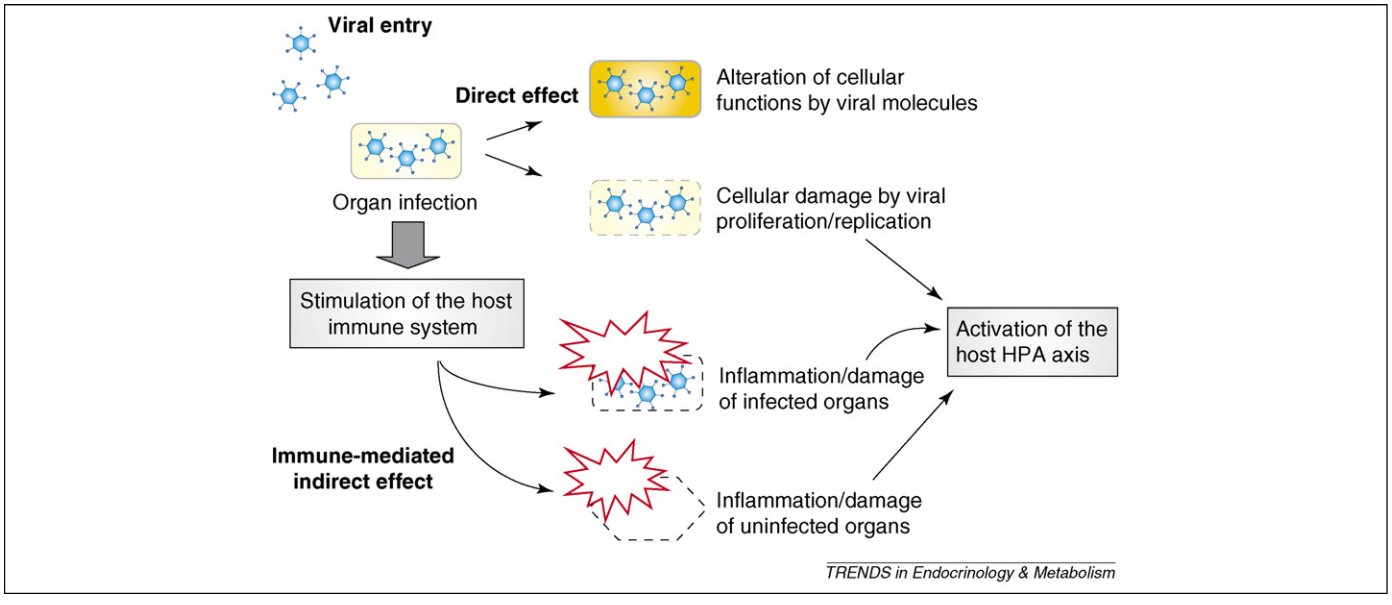

Figure 1. Virus-mediated modification of host endocrine organs. Viruses damage infected cells directly by proliferating inside cells, and can modulate cellular functions through molecules that are encoded by their genetic material. Viral infection might also trigger an inflammatory response, with consequent damage of both infected and uninfected tissues. Virus-induced tissue inflammation might increase the production of systemic mediators of inflammation, which, in turn, might stimulate the host HPA axis/stress system.