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Review article

Interferon and the central nervous system

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Abstract

Interferons (IFNs) were discovered as natural antiviral substances produced during viral infection and were initially characterized for their ability to "interfere" with viral replication, slow cell proliferation, and profound alteration of immunity. The IFNs are synthesized and secreted by monocytes, macrophages, T-lymphocytes, neurons, and glia cells. The different IFNs are classified into three classes: alpha, beta, and gamma. α-IFN produced in the brain exerts direct effects on the brain and endocrine system by activating the neurosecretory hypothalamic neurons and regulates the hypothalamic–pituitary–adrenocortical axis. IFNs modulate neurophysiological activities of many brain region involving in pain, temperature, and food intake regulation. α-IFN administration activates the sympathetic nerves innervating components of the immune system. IFNs may serve as regulatory mediators between the central nervous system, the immune system, and endocrine system. IFN is used as immunologic therapy to treat various hematologic malignancies and infectious ailments and autoimmune diseases.

Keywords: Interferon alpha; Beta; Gamma; Immune; Endocrine; Sleep; Food; Temperature; Glucose sensitive; Opiate; Naloxone

Contents

1. Introduction

Interferons (IFNs) are a family of naturally occurring complex proteins, glycoproteins and peptides that are synthesized and released by many vertebrates from fish to *Homo sapiens*. IFNs are produced in vivo by macrophages, monocytes, T lymphocytes, glia, and neurons (Larsson et al., 1978; Maruo, 1988; Plata-Salaman, 1991) at a constant "physiological" level. They act as intracellular messengers by altering the function of many different kinds of cells to induce and maintain physiological functions (Isaacs and Lindenmann, 1957; Marcovitz et

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al., 1984; Pestka et al., 1987; Baron et al., 1991; Bocci, 1988a,b, 1992). IFNs induce cell adhesion molecules that play an important role in development (Maroun, 1995), modulate cellular metabolism, and control growth and differentiation (Campbell et al., 1999). They also exert "cellular" effects such as antiproliferative effects on cells (Paucker et al., 1962), enhance the expression of immunologically relevant cell membrane constituents, and activate natural killer cells and macrophages, as well as possess anti-tumor effects (Isaacs and Lindenmann, 1957; Kirchner, 1984; Pestka et al., 1987; Baron et al., 1991; Bocci, 1988a, 1992). In addition, IFNs have high biological activity since cells of every species, from lower vertebrates to man, produce their own IFNs.

Interferons were discovered by Isaacs and Lindenmann (1957) in their antiviral experiments aiming to produce antiviral compound and to interfere with viral multiplication. They infected egg membranes with live viruses and discovered that the viruses failed to grow. They concluded that some forms of viral interference resulted from their treatment. They isolated the protein and named it "interferon" (IFN) since it interfered with viral growth. Interferons released into the bloodstream and intracellular fluid induce the production of an enzyme that counters the viral infection by preventing the viruses from replicating in the body (Bocci, 1992). Interferons bind to specific receptors on the cell surface and elicit a variety of cellular responses. The different IFNs were initially classified as leukocyte IFN, fibroblast IFN, and immune IFN according to their supposed production by a particular cell and organ site. Later, IFNs were classified into three different types on the basis of antigenicities of their proteins and biological properties: α-, β- and γ-IFNs (Bocci, 1985, 1988a,b; Bocci et al., 1985; Paulesu et al., 1985; Yasuda, 1993; Makino et al., 2000).

α-IFN is a protein with immunomodulatory, antiproliferative and antiviral properties. α-IFN plays a critical role in maintaining the balance of the immune system by stimulating natural killer cells. It is used in the treatment of hairy cell leukemia, AIDS-related kaposis, sarcoma, genital warts, and chronic hepatitis B and C. Exogenous α-IFN initially has been produced by infection of white blood cells in cultures (Kirchner, 1984; Pestka, 2000).

β-IFN is an immunoregulatory cytokine. It inhibits certain white blood cells, and is used mainly in the treatment of multiple sclerosis (MS), autoimmune neurites, and chronic inflammation demyelinating polyradiculoneuropathy (Creange et al., 1998; Hadden et al., 1999; Zou et al., 1999; Schaller et al., 2001; Pritchard et al., 2003; Vallat et al., 2003). β-IFN slows the growth of disease fighting white blood cells by stopping their production of myelin-destroying compound as well as correcting the deficiency of T cells that control the immune system. β-IFN is an important antiviral cytokine (Carr et al., 2003) because it stimulates the production of natural killer cells. In vivo, β-IFN is produced by fibroblasts that are stimulated by viruses or synthetic inducers (Pestka, 2000). α-IFN and β-IFN are also produced in response to viral infections to control herpes simplex virus type I (HSV-1) replication (Carr et al., 2003). Since β-IFN shares about 60% homology with α-IFN and since α-IFN and β-IFN exhibit many additional similarities, they are combined into one group known as type I IFNs.

γ-IFN was discovered several years after the discovery of α-IFN as an antiviral activity in the supernatant of human lymphocytes stimulated with mitogen. γ-IFN was the first lymphokine with its molecular structure identified. Lymphokines are defined as a substance produced by lymphocytes upon the activation of macrophages and act on the cellular components of the immune system such as T lymphocytes and thus lymphokines are immunoregulatory molecules (Kirchner, 1984). γ-IFN is a representative of two groups of biological important molecules, the lymphokines and the IFNs (Kirchner, 1984). γ-IFN is not structurally related to α-IFN or β-IFN (Adolf, 1985; Kubota et al., 2001). The γ-IFN is a macrophage activating protein that modulates a variety of biological pathways potentially relevant to muscle wasting and immune dysfunction. γ-IFN is predominantly produced by T lymphocytes and natural killer cells. It is also produced by astrocytes and microglial cells in the central nervous system (CNS) (De Simone et al., 1998; Xiao and Link, 1998; Kubota et al., 2001). γ-IFN regulates the immune system and responds to infectious agent by helping the body to fight infection and tumors (Gray and Goeddel, 1982; Kaur et al., 2003). It is used mainly to treat chronic granulomatous disease and osteopetrosis. γ-IFN is an activator of macrophages and natural killer cells; thus, it increases their anti-tumor activities, as well as regulates B cells immune responses and increases the secretion of the immunoglobins.

Due to the presence of the blood brain barrier, the brain is relatively isolated from the other organ systems, limiting the penetration of circulating lymphocytes and antibody to the brain (Darling et al., 1981). However, small amounts of IFNs have been reported to penetrate the brain (Cathala and Baron, 1970; Habif et al., 1975; Mattson et al., 1983; Vass and Lassmann, 1990). There is some evidence that IFNs enter the brain through areas lacking the blood brain barrier. Indeed, significant concentration of IFNs is found on sites such as the hypothalamus and pons, where the blood brain barrier is more permeable (Zimmerman and Krivoy, 1973; Scott et al., 1981; Bocci, 1985, 1992; Smith et al., 1985, 1986; Wiranowska et al., 1989). Since IFNs used in immunologic therapy are synthesized and released naturally in the body, they were thought to be nontoxic (Goldstein and Laszlo, 1988). However, several adverse effects were reported as a result of exogenous IFN treatment, such as insomnia, sensory and motor abnormality, fever, anorexia, flu-like symptoms, malaise, muscle pain (myalgia), depression, paraesthesia, amnesia, anxiety, dementia with apathy, cognitive dysfunction, confusion and depression (Scott et al., 1981). Wichers and Maes (2002) suggested that γ-IFN, α-IFN, and other cytokines induced side effects as a result of alteration of serotonin, noradrenergic, and hypothalamic–pituitary–adrenal systems. All of these symptoms are CNS mediated phenomena (Cantell et al., 1980; Mattson et al., 1983; Smedley et al., 1983; Ackerman et al., 1994; Iivanainen et al., 1985; Hori et al., 1991; Valentine et al., 1998; Schaefer et al., 1999). Therefore, this review will focus on the role of IFN on CNS activity.

2. Interferon classes and receptors

In general, the IFN family is divided into two groups — type I and type II IFNs. Type I IFNs consist of four major classes: α-IFN, β-IFN, ω-IFN, and τ-IFN, while γ-IFN belongs to type II IFNs (Pestka et al., 1987; Baron et al., 1991; Campbell et al., 1999; Pestka, 2000; Soos and Szente, 2003). The type I α-IFN and β-IFN (α/β-IFN) are comprised of the products of multiple α-IFN genes and a single β-IFN gene (Biron, 2001). Type I IFNs share a common receptor and exhibit similar biological activities. Ten separate species of α-IFN were identified during purification of leukocyte IFN (Pestka, 2000). The IFN receptors are ubiquitously distributed in various cell types. IFN receptors have been identified in the immune, endocrine, and central nervous systems (Aguet, 1980; Pestka et al., 1987).

Interferon receptors are found in macrophages, monocytes, T lymphocytes, glia, and neurons. Interferons modulate gene expression via a simple, direct signaling pathway containing Janus tyrosine kinases (JAK) and signal transducers and activators of transcription (STAT). Tyrosine kinase activation is a common mechanism for triggering eukaryotic signaling pathways (Schlessinger and Ullrich, 1992; Van der Geer et al., 1994; Yan et al., 1998). Binding of the IFNs to their cell surface receptors results in a complex cellular response associated with changes in the expression of a large number of genes (Samuel, 1991).

The IFN receptors have extracellular ligand-binding domain and intracellular kinase domain which are activated following ligand-induced dimerization (Walters et al., 1998; Pestka, 2000). α-IFN and β-IFN share the same receptor which composes of two subunits: AR1 and AR2 (Lewerenz et al., 1998; Maroun et al., 2000). These two subunits have α-/β-IFN ligand-binding properties (Stark et al., 1998; Maroun et al., 2000) and are coded by genes on mouse chromosome 16 and human chromosome 21 (Holland et al., 1997; Maroun et al., 2000). α-IFN binds to two JAK kinases, tyrosine kinase 2 (TYK2) and JAK1 (Colamonici et al., 1984; Novick et al., 1994; Domanski et al., 1997). This binding activates the JAK, STAT1, and STAT2 proteins (Muller et al., 1993; Silvennoinen et al., 1993; Barbieri et al., 1994; Colamonici et al., 1994) and stimulates transcription of genes containing the IFN-stimulated gene response element.

γ-IFN activates the JAK/STAT pathway through its α and β subunit receptors (Stark et al., 1998; Kaur et al., 2003) to activate JAK1 and JAK2 kinases followed by tyrosine phosphorylation of STAT1 (Shuai et al., 1993; Boehim et al., 1997; Stark et al., 1998; Kaur et al., 2003). γ-IFN receptor is composed of a ligand-binding subunit (GR1) and transducer subunit (GR2) coded by mouse chromosome 10 and human chromosome 21, respectively.

Several genes are involved in IFN action and are located in human chromosome 21. The "distal" half of chromosome 21 contains a large cluster of genes that direct the synthesis of IFN receptors and receptor components (Maroun et al., 1998). These genes (e.g., 2′5′-oligodenylate synthetase [2′5′-OAS], major histocompatibility class I [MHC-class], and RNA-dependent protein kinase) are responsible for the variety of actions perpetrated by the IFNs (Campbell et al., 1999). It was also demonstrated that antibodies to human chromosome 21-encoded cell surface components were able to block the action and binding of α-IFN to cells (Pestka, 2000). Direct proof that α-IFN R1 component is part of the type I receptor function was demonstrated by experiments disrupting the α-IFN R1 gene. For α-IFN R2, it was found that it binds to human gene α-IFN AR2 which is located on the αYAC that localizes on the 3×1S region of chromosome 21 (Novick et al., 1994; Yan et al., 1998).

The major pathway of intracellular signaling used by α/β-IFN and their receptors is by activating the signal transducer of transcription STAT1 and STAT2 to form a STAT1/STAT2 heteromer. STAT1/STAT2 complexes associate with a p48 protein identified as the IFN responsive factor 9 (IFR-9) forming the IFN-stimulating gene factor-3 (ISGF-3). ISGF-3 induces transcription as a result of recognizing IFN stimulated response elements (ISREs) in the promoter region of IFN responsive genes (Biron and Sen, 2001). The action of IFNs is mediated by interaction with specific cell surface receptors and the JAK–STAT signal transduction pathway (Langer and Pestka, 1988; Uzé et al., 1995; Pestka, 2000). Competitive binding studies found that type I IFNs (α- and β-IFN) share the same receptor complex, whereas the γ-IFN, which belongs to type II IFN, binds to another distinct receptor (Pestka et al., 1987; Li and Roberts, 1994; Pestka, 2000).

3. The central nervous system, the immune system and interferon

Reciprocal interactions between the CNS and immune system have gain new significance with the establishment of putative pathways of intercommunication between the CNS and immune system. This interaction occurs essentially at two levels: 1) cell to cell contact and 2) release of soluble mediators that bind to cell surface receptors (Hood et al., 1984; Cooper et al., 1986). Several morphological and physiological substrates were identified to provide the circuitry for reciprocal communication between these two systems (Besedovsky et al., 1977; Saphier et al., 1987, 1993, 1994, 1988; Dafny et al., 1988b; Dougherty and Dafny, 1991; Besedovsky and Del Rey, 2002). Immune-derived products, such as interleukins, endorphins, adrenocorticotrophic hormone (ACTH), and IFNs may possess neuromodulatory activities in addition to their immune-regulatory action (Ernstrom and Soder, 1975; Dafny et al., 1985a, 2004; Besedovsky et al., 1986; Smith et al., 1986; Felten et al., 1987; Dinarello, 1988, 1989; Blalock, 1989; Besedovsky and Del Rey, 2002). Moreover, it was reported that IFN modulates opiate mediated phenomena by a direct action within the CNS, thus directly supporting the contention that immune-derived peptide can convey information from the immune system to the CNS (Calvert and Gresser, 1979; Dafny, 1983a, b,c, 1998, 1999; Dafny et al., 1983, 1985a, 1989, 1996; Reyes-Vazquez et al., 1984a,b; Dougherty et al., 1986a,b; Dafny and Reyes-Vazquez, 1987; Reite et al., 1987). Several studies have demonstrated that α-IFN administration results in an alteration of the electrophysiological activity of brain

regions participating in pain suppression mechanisms and temperature and food-intake regulation (Hung et al., 1973; Dafny, 1983a, 1998; Prieto-Gomez et al., 1983; Reyes-Vazquez et al., 1984a,b; Dafny et al., 1985a; Nakashima et al., 1987, 1988; Birmanns et al., 1990). Some of the reports indicate that IFN modulates neuronal activity via opiate receptors while others postulate that the IFN does not appear to exert its effects upon opioid receptor but rather by an action upon a distinct receptor complex (Reyes-Vazquez et al., 1984a,b; Nakashima et al., 1987, 1988; Dafny et al., 1996; Dafny, 1998; 1999; Ikeda et al., 2003; Dafny et al., 2004; Kobayashi et al., 2004). Several reports suggest that α-IFN modulates single neurons in discrete CNS sites and modifies behavioral paradigms, supporting the concept that α-IFN is also a neuromodulator of immunologic origin (Bullock, 1985; Dafny et al., 1988a,b, 2004; Dunn and Crnic, 1992, 1993; Dafny, 1998).

In a series of behavioral experiments using morphine-dependent rats, α-IFN was given locally within the brain (intracerebroventricularly—i.c.v.) and systemically (i.p.) prior to naloxone injection, which precipitated withdrawal behavior. This α-IFN treatment attenuated dramatically the severity of opiate behavioral withdrawal signs (Dafny, 1983a,b,c; Dafny et al., 1983, 1985a,b, 1988b; Dafny and Reyes-Vazquez, 1987; Dougherty et al., 1987). Several electrophysiological recording procedures, such as sensory evoked potential, EEG, single neuron recording (Fig. 1), and microiontophoretic drug application and systemic application of IFNs, opioids and naloxone (Reyes-Vazquez et al., 1982, 1984a,b; Dafny, 1983a, b,c, 1985; Prieto-Gomez et al., 1983; Dafny et al., 1985a,b, 1988a,b; Birmanns et al., 1990) suggest that there are at least three different functional and/or receptor sites for α-IFN within the CNS: 1) a site where α-IFN caused excitation, which can be blocked/reversed by the opiate antagonist naloxone and may represent the κ or δ sites (Nakashima et al., 1987), 2) a site where α-IFN caused reduction (inhibition) in neuronal activities, which can be antagonized by naloxone and may present the μ receptor type, and 3) a site that α-IFN caused excitation in neuronal activity, but naloxone was unable to antagonize the α-IFN induced excitation (Reyes-Vazquez et al., 1984a; Dafny et al., 1985a). In an experiment using molecular procedure, it was demonstrated that i.c.v. injection of α-IFN

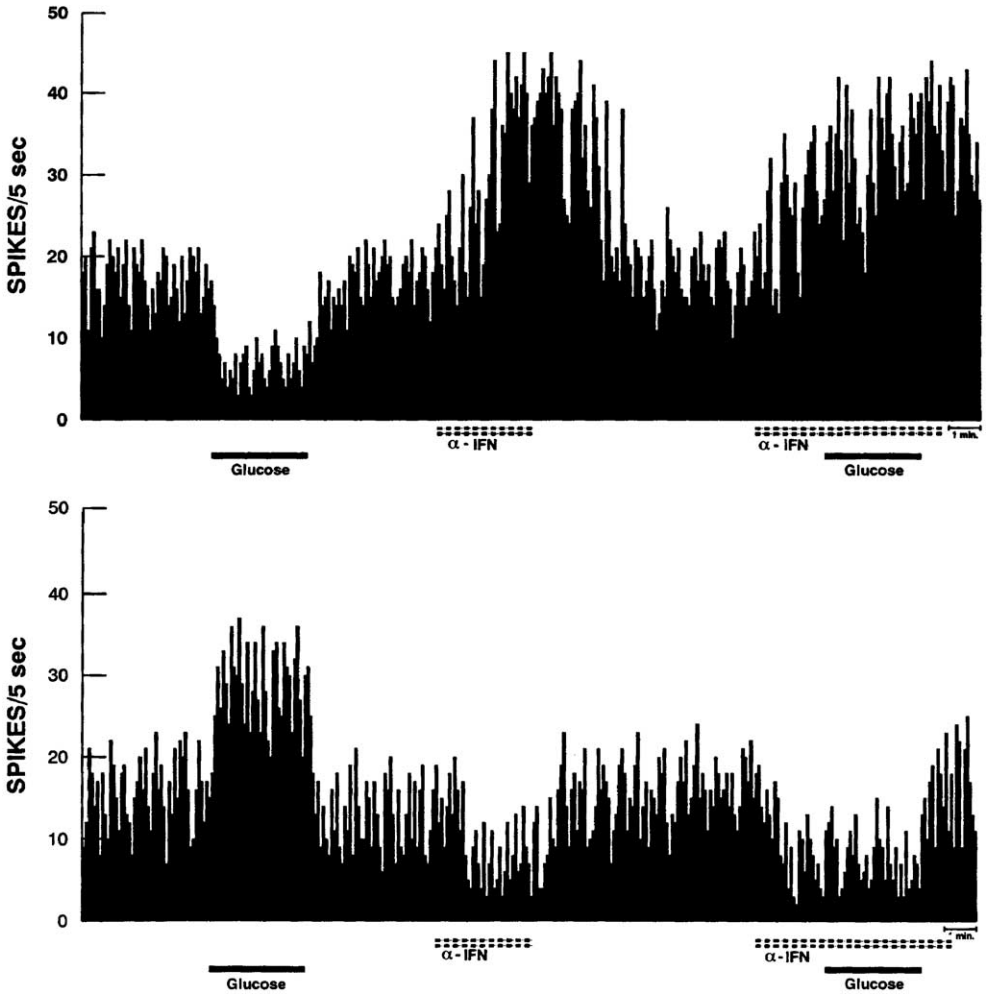

Fig. 1. Frequency histograms of representative neurons in ventromedial hypothalamus (VMH) and lateral hypothalamus (LH) following 10 mM glucose and 1500 IU α-IFN applied separately (left side) and together (right side). VMH (upper histogram) and LH (lower histogram) neuronal activities are modulated in a push–pull manner in regulating glucose sensitive neurons. Time between treatments is 60 min.

suppressed the cytotoxic activity of the cells in spleen of mice. This effect was prevented by pretreatment with naloxone (Take et al., 1992a,b; 1993). Moreover, in in vivo experiments using rat brain membrane preparations, α-IFN has been shown to inhibit the binding of [^{3}H] naloxone (Menzies et al., 1992), demonstrating a competition between α-IFN and naloxone for membrane binding sites. In conclusion, α-IFN is one of the cytokine products that possesses immunological and neuromodulatory properties and thus can be considered as one of the mediators that links the CNS and the immune system with each other.

4. The endocrine system and interferon

Stimulation of the immune system resulted in the production and release of several cytokines and hormones (Smith and Blalock, 1981; Hood et al., 1984; Smith et al., 1985, 1986; Späth-Schwalbe et al., 1989; Walters et al., 1998; Besedovsky and Del Rey, 2002). It was reported that leukocyte IFN provides an afferent link between the immune and the endocrine systems (Blalock and Smith, 1980; McCain et al., 1982). This conclusion was based on the detection of ACTH and endorphin-like substances from lymphocytes infected with the Newcastle disease virus. These were the first studies demonstrating that the immune system is producing peptides, and that these peptides interact with the neuroendocrine system (Blalock, 1989; Dinarello, 1989; Reder, 1992). Moreover, it was shown that α-IFN shares a common binding site to specific receptors such as ACTH (Aguet, 1980; Blalock and Stanton, 1980; Blalock and Smith, 1981a,b; Aguet and Mogensen, 1983). Cytokine production including α-IFN is not restricted to the immune cells (Blalock, 1989; Dinarello, 1989; Reder, 1992). Several neuronal components in specific brain areas are producing α-IFN and exert direct effects on the CNS, as well as on the endocrine system (Dinarello, 1989; Kidron et al., 1989; Reder, 1992).

Sequential similarities between α-IFN, ACTH and melanotrophic stimulation hormone (MSH) have been reported (Vernikos-Danellis et al., 1977; Carelli et al., 1982; Krueger et al., 1982; Root-Bernstein, 1984). These structural similarities may explain the presence of common functional characteristics found between MSH, ACTH, α-IFN, and immunological activity. Moreover, α-IFN injection stimulates ACTH production and secretion (Blalock and Smith, 1980; Smith and Blalock, 1981; Root-Bernstein, 1984; D'Urso et al., 1991). Systematic (i.p.), central (i.c.v.), and local (microiontophoretic) treatment of α-IFN within the paraventricular hypothalamic nucleus inhibits the hypothalamus–pituitary–adrenocortical axis (Kidron et al., 1989; Saphier et al., 1993, 1994), such as the glucocorticoid hormones which modulate immune activity (Reder, 1992; Saphier et al., 1994). It was demonstrated in electrophysiologically identified neurosecretory neurons of the paraventricular hypothalamic nucleus, which regulates adrenocortical secretion, that α-IFN administration decreased their neuronal activities, indicating that α-IFN participated in the regulation of adrenocortical releasing and/or secretion via the paraventricular hypothalamic nucleus neurons (Saphier et al., 1988, 1994). Moreover, some environmental cues such as stress and mental disorders alter the endocrine and immune systems which in turn produce α-IFN. These productions of α-IFN resulted in stimulating the neuronal activity of the CNS to modulate the neuroendocrine system and thereby providing a feedback to regulate the immune system (Besedovsky et al., 1975, 1977; Bullock, 1985; Dafny et al., 1985a,b; Besedovsky and Del Rey, 2002; Felten et al., 1987; Solomon, 1987; Saphier et al., 1987, 1988, 1994; Dunn, 1989). In conclusion, these observations indicate that the immune system, endocrine system, and the CNS communicate with one another (Bullock, 1985; Besedovsky and Del Rey, 2002; Felten et al., 1987; Solomon, 1987; Dunn, 1989).

5. Drowsiness, sleep and interferon

Cytokines such as IFN treatment are somnogenic and are involved in the sleep–wake regulation (Shoham et al., 1987; Krueger and Majde, 1995; Spath-Schwalbe et al., 2000; Cadinali and Esquifino, 2003). Most living organisms exhibit behavioral and physiological rhythms with a cycle of about 24 h that is regulated by an internal time-keeping system called the circadian clock, which acts like a multifunctional timer in regulating the homeostatic system, such as sleep and wakefulness (Koyanagi and Ohdo, 2002). The area of the central nervous system that is involved in the regulation of time is the hypothalamus. The hypothalamic nucleus that regulates the circadian clock is the suprachiasmatic nucleus, which is considered as the master clock. The suprachiasmatic nucleus has projections in multiple hypothalamic and extrahypothalamic nuclei that are involved in controlling specific functions that exhibit daily rhythms.

Several clock genes regulating a vast array of circadian rhythms have been identified. Three clock genes (*Per 1*, *Per 2*, and *Per 3*) were identified to rhythmically express in the suprachiasmatic nucleus. The core circadian oscillator is composed of interacting positive and negative transcription–translation feedback loops. The CLOCK:BMAL1 heterodimers bind to the E-box enhancer element and are subsequently suppressed by complexes of *Per* and *Cry* proteins (Gekakis et al., 1988; Kume et al., 1999; Koyanagi and Ohdo, 2002). The transcriptional machinery of the core circadian clockwork also regulates the output rhythms of the master clock, i.e., CLOCK:BMAL1 heterodimers act through an E-box enhancer to activate the transcription of vasopressin prepropressophysin, albumin D-element binding protein, and prokineticin 2 mRNAs, showing a specific circadian output function (Jin et al., 1999; Ripperger et al., 2000; Cheng et al., 2002; Koyanagi and Ohdo, 2002). α-IFN has the ability to modulate the master clock (suprachiasmatic nucleus) at the genetic level of the *Per 1* gene (Ohdo et al., 2001), the gene associated with an altered rhythmicity of clock gene expression and decreased CLOCK and BMAL1 protein levels in the suprachiasmatic nucleus (Koyanagi and Ohdo, 2002). The decreased CLOCK and BMAL1 protein levels in suprachiasmatic nucleus following α-IFN treatment prevent oscillation in the expression of clock and clock-controlled output genes and modulate the core circadian

oscillation mechanism (Koyanagi and Ohdo, 2002). This finding may explain the changes in EEG activity following α-IFN (Dafny, 1983a; Birmanns et al., 1990) and the insomnia disturbance of sleep onset (Smedley et al., 1983; Meyers and Valentine, 1995). Additional explanation for the insomnia effect of IFN is due to the significant increase in the melatonin level and thereby delayed the peak melatonin concentration for several hours as a result of IFN treatment (Uchimura et al., 1999). Melatonin is known to regulate the sleep–wake cycle.

Insomnia is the inability to obtain normal amount of sleep necessary to maintain daytime behavior. Disruption of the normal circadian rhythms is one of the causes that elicit insomnia. Narcolepsy is a complex debilitating disorder of sleep regulation characterized by intermittent excessive daytime sleepiness, cataplexy, sleep paralysis and hypnagogue/hypnopompic hallucinations (Wieczorek et al., 2004). There is strong evidence that the orexin (hypocretin) neurotransmitter system is involved in the pathogenesis of narcolepsy and that the prepro-orexin gene binds to α-IFN receptors and acts as a transcription factor to exert excessive daytime sleepiness (Chemello et al., 1999; Wieczorek et al., 2004).

The somnogenic actions of α- and β-IFN have been reported a long time ago (Smedley et al., 1983; Krueger et al., 1987; Meyers and Valentine, 1995; Pavol et al., 1995). However, it was only recently found that the suprachiasmatic nucleus contains γ-IFN receptors (Cadinali and Esquifino, 2003) and that γ-IFN, in dose-dependent characteristics, increases non-rapid eye movement sleep (non-REM) accompanied by slow wave EEG activity (Kubota et al., 2001). Changes in sleep pattern are common symptoms of infectious diseases. The initial sleep alteration induced by infection is an increase in non-REM sleep and delta wave activity of the EEG (Krueger et al., 1987; Fang et al., 1995; Kubota et al., 2001). Similar observation was obtained following α- and β-IFN injection (Dafny, 1983a; Krueger et al., 1987; Birmanns et al., 1990; De Sarro et al., 1990; Kimura-Takeuchi et al., 1992; Krueger and Majde, 1995). Men with difficulty in maintaining normal sleep had a significantly lower γ-IFN to IL-4 ratio (Sakami et al., 2002). Alcoholic subjects show profound sleep disturbances. Their γ-IFN ratio between IL-10 shows a lower ratio and a reduced level of natural killer cell activity coupled with losses of delta sleep and increased REM sleep (Redwine et al., 2003). γ-IFN receptors were identified in the suprachiasmatic nucleus (Kubota et al., 2001; Redwine et al., 2003), which is the master clock that regulates the central circadian pacemaker. In conclusion, IFNs exert disruptive effects on the clock-gene mRNA expression and modulate the circadian rhythms of locomotor activity and temperature, as well as the hormonal pathway that regulates the circadian secretion of melatonin and the sleep–wake cycle.

6. Anorexia, food intake and interferon

The brain areas that regulate and control food intake are thought to be the ventromedial hypothalamus, lateral hypothalamus, and paraventricular hypothalamic area (Dafny and Jacobson, 1975; Tempel et al., 1993; Oomura, 1988; Dafny et al., 2004). The lateral hypothalamus is considered as “a center involved in initiating feeding” (Schanzer et al., 1978; Morley, 1987) or “a feeding center” involved in initiating food intake (Oomura, 1988; Reyes-Vazquez et al., 1994; Dafny et al., 2004). The ventromedial hypothalamus is considered to be responsible for producing the sensation of fullness and is also called “a satiety center” (Schanzer et al., 1978; Morley, 1987; Dafny et al., 2004).

Several humoral peptides are involved in the hypothalamic regulation of food intake. These peptides are key signaling molecules that promote either feeding or satiety, as well as an antagonism to food intake. They are divided into anabolic peptides that promote feeding and catabolic or anorexigenic peptides that inhibit feeding. The anabolic peptides include leptin, insulin, glucose, cholycystokinin, neuropeptide Y, agouti-related protein, melanin-concentrating hormone, orexin, and galumin. The anorexigenic peptides include α-melanocyte stimulating hormone, cocaine and amphetamine-regulated transcript, glucose-like peptides 1 and 2, and prolectin releasing peptide (Woods and Stricker, 1999). Patients and animals treated daily with α-IFN show prominent side effects such as anorexia and lose of more than 10% of their body weight (Mattson et al., 1983; Rohatiner et al., 1983; Smedley et al., 1983; Bocci, 1985; Dafny and Reyes-Vazquez, 1985; Quesada et al., 1986; Dantzer et al., 1987; Fent and Zbinden, 1987; Morley, 1987; Adams et al., 1988; Dafny et al., 1988a; Saphier et al., 1988; Plata-Salaman, 1989; Segall and Crnic, 1990; Crnic and Segall, 1992; Reyes-Vazquez et al., 1994; Meyers and Valentine, 1995; Pavol et al., 1995). The anorexic state produced by α-IFN is reversible. All patients return to normal weight within 7 to 10 days after discontinuation of α-IFN therapy (Rohatiner et al., 1983).

Eating is a regulatory behavior that contributes to caloric homeostasis. Food intake provides nutrients to support the continuous energy demands as well as maintains a stable body weight. Indeed, local application of α-IFN on ventromedial hypothalamus and lateral hypothalamus neurons using micro-iontophoretic procedure and simultaneously recorded from these areas (Reyes-Vazquez et al., 1982, 1984a; Prieto-Gomez et al., 1983; Dafny et al., 1985a, 1996) resulted in opposite responses, i.e., decreased activity of lateral hypothalamus neurons and increased ventromedial hypothalamus neuronal activity. Similar observations were obtained from simultaneous single cell recordings from coronal brain slices containing both the ventromedial hypothalamus and the lateral hypothalamus areas (Reyes-Vazquez et al., 1997). The mechanisms by which cytokines induce anorexia are considered to be multifactorial (Hori et al., 1991). Cytokines are known to suppress food intake independently and to elicit fever. However, increase in body temperature may inhibit feeding by modulating the ventromedial hypothalamus and lateral hypothalamus neurons (Nakayama et al., 1981; Hori et al., 1988).

Many reports (Dafny, 1983a; Krueger et al., 1987; Färkkilä et al., 1988; Saphier et al., 1988; Birmanns et al., 1990; De Sarro et al., 1990; Plata-Salaman, 1991) suggest that immunoregulators such as interleukins and IFNs induce sleep. Sleep prevents eating and results in weight loss. It is evident that

cytokine-induced anorexia involves both peripheral and CNS mechanisms. Cytokines modulate gastrointestinal activities, cause metabolic changes, and modulate the endocrine system and neuropeptide/neurotransmitter levels in the hypothalamus that result in modulating eating behavior (Plata-Salamán et al., 1988; Plata-Salaman, 1992, 1998). The direct effect of glucose sensitive neurons (Reyes-Vazquez et al., 1994) in push–pull manner in the ventromedial hypothalamus and lateral hypothalamus may cause profound changes in the eating patterns of animals and humans (Plata-Salaman, 1998). In conclusion, these reports collectively suggest that the loss of appetite is directly related to α-IFN therapy.

7. Fever, temperature and interferon

Regulation of core temperature is essential since most of the metabolic processes necessary for life are temperature-dependent. The preoptic/anterior hypothalamus area contains three types of neurons sensitive to cold, heat, and different degrees of temperature. These neurons are involved in determining the temperature set-point. Therefore, the preoptic/anterior hypothalamus area is suggested as the site of temperature regulation (Ackerman et al., 1994; Dinarello et al., 1984).

Fever is a host's defensive response to various exogenous pathogenic organisms or their products such as lipopolysaccharides. It is mediated centrally by endogenous pyrogens such as the IFNs family (Blatteis et al., 1991). The terms "granulocytic" and "endogenous pyrogen" were used to describe substances with biological properties of fever induction. It became evident that pyrogenicity is a fundamental biologic property of several cytokines, including the IFNs family (Dinarello, 1999; Leon, 2004). The production of the pyrogenic endogenous cytokine resulted from the host defense response to the various exogenous pathogenic organisms (Blatteis et al., 1991) that leads to hypothermia. Hypothermia is a thermoregulatory response to systemic inflammation that is often reported as maladaptive to the host. The mechanisms regulating hypothermia are not fully understood, but different cytokines including α-IFN and γ-FN have been shown to induce or modulate hypothermia (Leon, 2004). Injection of α-IFN intravenously (i.v.) or i.c.v. in rodents, cats, and rabbits elicits fever without the production and involvement of the natural endogenous pyrogenic substance such as interleukin 1 (IL-1), which suggests that α-IFN is an endogenous pyrogen (Dinarello et al., 1984; Dinarello, 1988, 1989). α-IFN modulates fibrile responses by activating the thermosensitive and the thermally insensitive preoptic/anterior hypothalamus neurons. It inhibits the warm-sensitive neurons and stimulates and increases the activity of the cold-sensitive neurons but has no effects on thermally insensitive neurons (Dantzer et al., 1987; Farrar et al., 1987; Nakashima et al., 1988; Saphier et al., 1988; Kidron et al., 1989; Kuriyama et al., 1990; Blatteis et al., 1991; Hori et al., 1991; Shibata and Blatteis, 1992). The fever induced by IFN may be explained, at least in part, by the effects of IFN on preoptic/anterior hypothalamus thermosensitive neurons (Nakashima et al., 1988). In addition, this led to the postulate that IFN in the brain produces fever by a two-step mechanism: first by the immediate action on preoptic/anterior hypothalamus thermosensitive neurons and subsequently by the release of prostaglandin, which elicits fever (Hori et al., 1988; Blatteis et al., 1991; Hori et al., 1991).

The rise in body temperature may also involve food intake modulation by affecting glucose-responsive neurons in the lateral hypothalamus and ventromedial hypothalamus, which results in energy expenditure and reduced food intake (Murray and Murray, 1979; Dinarello et al., 1984; Hori et al., 1991). On the other hand, Dougherty et al. (1986b) reported that α-IFN has no effect on baseline temperature or morphine induced hypothermia, suggesting that temperature alterations are not responsible for the action of α-IFN on weight loss or on food intake suppression.

8. Hypothalamic glucose sensitive neurons and interferons

Interferon treatment suppresses food intake in humans and animals (Mattson et al., 1983; Bocci et al., 1985; Hori et al., 1991; Meyers and Valentine, 1995). Food intake provides nutrients to support the continuous energy demands that contribute to caloric homeostasis as well as maintains a stable body weight. Two major hypotheses have been put forth to account for feeding and the process by which the usual balance in caloric intake is established: 1) the depletion–repletion hypothesis and 2) the primed response hypothesis. The depletion–repletion hypothesis is based on the idea of caloric set-point regulated by hypothalamic ventromedial hypothalamus and lateral hypothalamus glucose sensitive neurons. The ventromedial hypothalamus glucose sensitive neurons may be responsible for the production of fullness sensation (satiety center), while the lateral hypothalamus glucose sensitive neurons are involved in initiating food intake (Schanzer et al., 1978; Morley, 1987; Oomura, 1988). The lateral hypothalamus and ventromedial hypothalamus glucose sensitive neurons sense endogenous metabolic parameters and participate in the control of food intake and energy balance (Hori et al., 1988; Oomura, 1988; Kuriyama et al., 1990; Hori et al., 1991). When these neurons are challenged with α-IFN, the lateral hypothalamus glucose sensitive neurons are inhibited, while the ventromedial hypothalamus glucose sensitive neurons (Fig. 1) are facilitated (Mattson et al., 1983; Prieto-Gomez et al., 1983; Dafny et al., 1985a; Kow and Pfaff, 1985; Hori et al., 1988, 1991; Plata-Salaman, 1989, 1991; Reyes-Vazquez et al., 1994). This observation can explain how IFN elicits feeding suppression and anorexia (Mattson et al., 1983; Krueger et al., 1987; Hori et al., 1991). Other cytokines, such as tumor necrosis factor (TNF) or IL-1, exert similar effects of IFN in inhibiting glucose sensitive neurons in the so-called "hunger center" or lateral hypothalamus, which results in suppression of feeding (Kow and Pfaff, 1985; Plata-Salaman, 1989, 1991). Most of the glucose sensitive neurons are also sensitive to the TNF, IL-1 and α-IFN (Hori et al., 1988, 1991; Plata-Salaman, 1989, 1991).

The ventromedial hypothalamus and lateral hypothalamus areas are also known to contain neurons which sense metabolic parameters, such as glucose, and participate in regulating and controlling energy balance (Dafny and Jacobson, 1975; Ono et al., 1980; Oomura, 1988; Tempel et al., 1993; Dafny et al.,

2004). In addition, the hypothalamus also acts as a neuroendocrine transducer site in relation to the control of food intake involving a balance between a number of neuropeptides and neurotransmitters (Dafny et al., 2004). In addition, a variety of immunoregulator products act directly in the CNS to regulate food intake (Reyes-Vazquez et al., 1984a; Plata-Salaman, 1989; Plata-Salaman, 1991). In experiments using local application of α-IFN and single lateral hypothalamus and ventromedial hypothalamus neurons recording, opposite effects between the lateral hypothalamus and the ventromedial hypothalamus were observed (Prieto-Gomez et al., 1983; Dafny et al., 1985a,b). Reciprocal interaction between lateral hypothalamus and ventromedial hypothalamus in mechanisms of hunger and satiety was reported (Schanzer et al., 1978), suggesting that there is a push–pull interaction between the lateral hypothalamus and ventromedial hypothalamus. The data using α-IFN verified this reciprocal manner in food regulation (Reyes-Vazquez et al., 1994).

Simultaneously behavioral and electrophysiological experiments studying lateral hypothalamus glucose sensitive neurons and food intake in freely behaving rats previously implanted with permanent electrode (Reyes-Vazquez et al., 1994) demonstrated that three weeks of α-IFN treatment elicited a reversible dose-related decrease of both food intake and body weight. The loss of weight as a result of decrease in food intake resulted from daily α-IFN injection for three weeks was correlated with decreased neuronal activity in the glucose lateral hypothalamus sensitive neurons (Reyes-Vazquez et al., 1994). Similar observations were obtained when the α-IFN was injected systemically (i.p.) or locally in the ventricle (i.c.v.). This observation suggests that α-IFN suppresses food intake by suppressing the neuronal activity of the lateral hypothalamus glucose sensitive neurons (Reyes-Vazquez et al., 1994).

In experiments using ventromedial hypothalamus brain slices and recording neuronal activities from glucose sensitive neurons following α-IFN treatment, Kow and Pfaff (1985) showed that this glucose sensitive neurons were modulated by α-IFN. Moreover, when naloxone, a morphine antagonist, was added to the preparation, the α-IFN effects were prevented, suggesting an opioid-like effect by the α-IFN. To answer this question, Reyes-Vazquez et al. (1984a) used an experimental preparation known to contain opiate receptors in this procedure and showed that naloxone reversed the opioid effects but not the α-IFN effect. This observation led the investigators to suggest that α-IFN does not exert its food intake suppression effects via opiate receptors.

Although cytokine such as IFN suppresses food intake independently to fever, it is suggested that the increase in temperature by IFN treatment may be one of the reasons that inhibits feeding, since fever also modulates the activity of glucose-responsive neurons in the ventromedial hypothalamus and lateral hypothalamus (Nakayama et al., 1981; Hori et al., 1988). Because IFN produces sleep and sleep prevents eating, less eating caused weight loss. This is another possible explanation of how IFN affects feeding behavior (Dafny, 1983c; Krueger et al., 1987; Saphier et al., 1988; De Sarro et al., 1990; Birmanns et al., 1990; Plata-Salaman, 1991). Furthermore, in healthy subjects, plasma IFN level is increased during the day with peak level at 18:00 h and the lowest level in early morning (Bocci, 1985; Bocci et al., 1985; Paulesu et al., 1985). These daily variations in the endogenous IFN level in healthy humans are linked to external cues such as physical activity, feeding, and sleep (Paulesu et al., 1985). In conclusion, these reports suggest that the IFN regulate glucose sensitive hypothalamic neurons involved in food-intake regulation.

9. Opiate and interferon

Morphine treatment inhibits the secretion and reduces the level of circulating endogenous α-IFN (Gober et al., 1975; Hung et al., 1973), as well as decreases the capability of cells to produce α-IFN (Vilcek et al., 1968). The degree of α-IFN reduction was dose-dependent, i.e., with increased morphine dose, more decrease in α-IFN circulating level was observed (Hung et al., 1973). Moreover, α-IFN shares some pharmacological properties similar to β-endorphin, such as the production of analgesia and catatonia and affinity for [^{3}H] morphine binding sites in mouse brain membrane (Blalock and Smith, 1980, 1981a; Jiang et al., 2000). β-endorphin and metenkephalin increase the production of endogenous γ-IFN (Brown and VanEpps, 1986). Other evidence linking α-IFN with opioids is provided by experiments showing that lymphocytes stimulated α-IFN inducers to produce ACTH and endorphin-like substances. Further, they exhibited a similar antigenic reaction, suggesting that these peptides have some common structural properties (Blalock and Smith, 1980, 1981a,b; Blalock and Stanton, 1980; Smedley et al., 1983; Root-Bernstein, 1984; Saphier et al., 1987, 1988, 1994; De Sarro et al., 1990; Shibata and Blatteis, 1992), as well as an affinity to [^{3}H] morphine binding site in brain membranes preparation (Janicki, 1992) and that α-IFN inhibits the binding of [^{3}H] naloxone, ^{3}H-D-Ala^2, D, Leu^5 enkephalin (DADLE) (Blalock and Smith, 1981a; Menzies et al., 1992).

Tolerance, physical dependence, and abstinence syndrome (behavioral withdrawal) are common outcomes of repetitive use of opiate (Jaffe and Martin, 1990; Jaffe, 1990). These behavioral manifestations represent a fundamental feature of the addictive process. Physical dependence (addiction) on opiates can be quantified by the intensity and frequency of the behavioral withdrawal signal observed after abrupt termination of opiate intake or after precipitated withdrawal resulted from treatment with an opiate antagonist, such as naloxone (Jaffe, 1990). The intensity and frequency of the withdrawal behavior are used as indicators to quantify the degree of addiction.

Since the discovery of the endogenous opiates, the question that arises is what mechanism prevents the development of tolerance and/or dependence to these endogenous opioids. It was postulated that endogenous production of a protein, a peptide, or a cytokine in the CNS could prevent the development of tolerance or physical dependence to these circulating endogenous opiates (Zimmerman and Krivoy, 1973; McCain et al., 1982; Dafny, 1984, 1985). Bertolini et al. (1981) suggested that

some endogenous substances are produced and released along with the endogenous opioids in order to prevent the organism from developing tolerance to or dependence on its own endogenous opioids.

The above observations were the rationale for a series of experiments to test the following hypothesis: α-IFN is one of the endogenous substances which serves to prevent the development of tolerance and/or dependence to the endogenous opioids (Prieto-Gomez et al., 1981; Reyes-Vazquez et al., 1982, 1984a,b; Dafny, 1983a,b, 1984, 1985; Dafny et al., 1983, 1985a,b, 1988a,b; Prieto-Gomez et al., 1983; Dafny and Reyes-Vazquez, 1985, 1987; Dougherty et al., 1986a,b, 1987; Dougherty and Dafny, 1991). α-IFN was given 1 h before chronic morphine treatment or after chronic morphine treatment but at 1 h prior to naloxone injection to precipitate withdrawal, aiming to observe whether the IFN treatment would reduce the severity of the behavioral withdrawal. Indeed, these experiments demonstrated that α-IFN prevented the development of tolerance and reduced the severity of the opiate withdrawal syndrome (Dafny, 1983a,b; Dafny et al., 1983, 1985a,b, 1988a, b; Dafny and Reyes-Vazquez, 1985, 1987; Dougherty et al., 1986a,b, 1987; Dougherty and Dafny, 1991; Kugaya et al., 1996). These observations suggest that α-IFN is one of the endogenous substances that prevents the development of tolerance and physical dependence to the endogenous opioids. Whatever the α-IFN mechanism is, its ability to modify the development of tolerance and the severity of the opiate withdrawal syndrome suggests that α-IFN participates to maintain homeostasis in morphine-dependent subjects (Dafny, 1984, 1985, 1998).

The involvement of the immune system in some of the various aspects associated with the chronic use of opioid was suggested a long time ago by Andral in 1844 and others (Cohen et al., 1965; Meisheri and Isom, 1978; Dafny et al., 1988a). Cells of the immune system possess opiate receptors (Hazum et al., 1979) which when activated would induce a variety of functional modifications such as the establishment of profound immune suppression following chronic opiate treatment (Pellis et al., 1986; Jaffe, 1990). Morphine treatment suppresses immune functions (Dafny et al., 1985a,b). Morphine can modulate directly the immune system via binding to μ, κ or δ opioid receptors on immune cells (Roy and Loh, 1996). While α-IFN has shown to activate δ and κ opioid receptors (Kobayashi et al., 2004), morphine can also modulate the immune system indirectly via an alteration in the activity of non-immunological system (Peterson et al., 1993), such as the hypothalamic–pituitary–adrenocortical endocrine system. α-IFN binds to opiate receptors and shares some pharmacological properties of the opiates, such as production of analgesia, catatonia and altering locomotor activity. These effects are reversed or prevented by naloxone (Blalock and Smith, 1981a; Dougherty et al., 1986a,b, 1987; Blalock, 1989; Birmanns et al., 1990; De Sarro et al., 1990; Jiang et al., 2000). α-IFN inhibited cAMP accumulation by forskolin in ^{3}H-SYSY cells expressing μ and δ opioid receptors as well as modulated serotonin, glutamate and opioid (Saphier et al., 1994; Jiang et al., 2000; Schaefer et al., 2003), while γ-IFN regulated morphine μ opioid receptors by modulation of two distinct cAMP-dependent pathways (Wang et al., 2003). Moreover, the side effects produced by IFN therapy can be reversed by the opiate antagonist naltroxane (Valentine et al., 1995).

The ability of the immune system and the CNS to communicate and interact with each other was demonstrated (Dafny et al., 1985a,b, 1988b, 2004; Saphier et al., 1987, 1988, 1993, 1994; Blalock, 1989; Dafny et al., 1996; Dafny, 1998). Moreover, it was shown that CNS lesions or ablations (e.g., the hypothalamus) modulate immune components and its reaction to infection (Jankovic and Isakovic, 1973; Spector and Korneva, 1981). Hypothalamic neurons alter their neuronal firing rates following an immune challenge (Besedovsky et al., 1977; Spector and Korneva, 1981). It was demonstrated that several immunomodulating agents, such as IFN, (Dafny, 1983a,b,c, 1997, 1998; Dafny and Reyes-Vazquez, 1987; Dafny et al., 1985a,b, 2004), cyclosporine A (Dafny et al., 1985b), cortisol, and cyclophosphamide (Montgomery and Dafny, 1987) modulate the severity of naloxone precipitated opiate withdrawal in morphine-dependent rats, providing additional evidence that the immune system and immunomodifiers participate in opiate activities.

The development of opiate dependence and the expression of withdrawal are associated with the activity of specific brain regions (Jaffe and Martin, 1990). Lesioning of these sites prevents the acute response to morphine as well as the development of morphine physical dependence (Kerr and Pozuelo, 1971; Teitelbaum et al., 1974). Direct chronic injections of opioid into these brain sites elicit a state of physical dependence similar to that observed following chronic systemic injection of opiates (Wei, 1971; Laschka et al., 1976). The withdrawal behavioral and the neuronal activity of the above brain sites that were modulated following systemic or local IFN application or manipulation of the immune system suggest a strong interaction between IFNs and the opioid system (Jankovic and Isakovic, 1973; Spector and Korneva, 1981; Reyes-Vazquez et al., 1982, 1984a, 1994, 1997; Dafny, 1983a, 1999; Prieto-Gomez et al., 1983; Dafny et al., 1985a,b).

10. Clinical use of IFN

Administration of IFN has a wide range of efficacy in hematological malignancies, including tumors of presumed B cell, T cell, and myeloid lineages, kaposis sarcoma, lymphoma, polycythemia vera, chronic myelogenous leukemia, hairy cell leukemia, virus infection, hepatitis C, hepatitis B, and multiple sclerosis (Dafny et al., 2004). Multiple sclerosis is an autoimmune disease. It occurs when the body's immune system attacks the body's own myelin. Damage to the myelin compromises the CNS functions. β-IFN was used successfully in reducing the number and severity of multiple sclerosis attacks. β-IFN slows the growth of the disease by stopping the production of myelin-destroying compounds. Therefore, IFN may serve as a regulatory mediator in the brain, the endocrine system, and the immune system. Immunological therapy uses IFN to treat various hematological malignancies and infectious ailments, as well as autoimmune diseases. Overall, the IFNs

have surprisingly wide application in biology because of their pleotropic activity (Dafny et al., 2004).

11. Conclusion

Cytokines are synthesized and secreted in physiological levels by macrophages, leukocytes, monocyte, T lymphocytes, glia, and neurons as well as in response to viral infection. Subsequently, they are known to be diverse biological response modifiers and participate in many physiological activities and as inhibitor of viral proliferation, anti-tumor activity and enhancement to immune functions. This review focuses on one family of cytokines, the IFNs, and summarizes reports showing that there are several IFNs and receptors. IFNs participate in the regulation of various cellular processes and exert an effect on the endocrine system, immune system, and CNS (Aguet, 1980; Blalock and Smith, 1981a,b; Aguet and Mogensen, 1983; Dafny et al., 1985a,b, 2004; Morley, 1987; Pestka et al., 1987; Dafny, 1998; Besedovsky and Del Rey, 2002). The IFNs produced in the brain exert direct effects on the hypothalamus as well as regulate the endocrine system via the hypothalamic–pituitary–adrenocortical axis by activating the corticotrophin-releasing factor via a positive feedback effect. Numerous studies show sequential similarities and cross reactivity among IFN, ACTH, and MSH which explain the common functional characteristics between immunological activity, IFN and MSH-ACTH like activity. The IFNs participate as an arm of the immune system and alter the thermoregulator centers in the preoptic/anterior hypothalamus neurons to fight infections and to regulate the thermosensitive neurons. The IFNs modulate the reticular activating system and different hypothalamic areas. The effects of IFNs on the suprachiasmatic nucleus are to modulate the sleep–wake cycle. The effects of IFNs on the ventromedial hypothalamus and lateral hypothalamus are to modulate food intake. In addition, the review summarizes the evidence that IFNs participate in the regulation of glucose sensitive neurons in the ventromedial hypothalamus and lateral hypothalamus in a push–pull manner. The last paragraph of this review summarizes the similarity between IFNs and endogenous opiates, and the possibility that IFNs are the endogenous cytokines produced to prevent the development of tolerance to or dependence on the endogenous opioid.

Interferon and opioid receptors were identified on various components of the immune system (Hazum et al., 1979; Wybran et al., 1979; Lopker et al., 1980; Gilman et al., 1982). Opioids alter the percentage of T cells in the peripheral blood of humans (Wybran et al., 1979), the reactivity to T cells to mitogenic stimulation by lectins (c) is impaired in cells from opiate users. Natural killer and T lymphocyte activities are suppressed in opiate mediated stressed animals (Shavit et al., 1984). Moreover, it was shown that administration of morphine resulted and decreased the level of circulating endogenous α-IFN, as well as decreasing the capability of cells to produce α-IFN (Vilcek et al., 1968). The level of this inhibition was directly related to the morphine dosage (Hung et al., 1973). These studies suggest that the immune system or immune cell product acts on the CNS and is involved in regulating function, such as the opiate mediated response (Dafny, 1999), suggesting that there is a reciprocal pathway of communication between the immune system and the CNS (Dafny, 1998).

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