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Interferon modulates glucose-sensitive neurons in the hypothalamus

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Abstract Interferon-α (IFN) therapy induces feeding suppression that resembles anorexia. The hypothalamic glucose-sensitive neurons engage in feeding behavior. Coronal sections of rat brains, containing both the lateral hypothalamus (LH) and the ventromedial hypothalamus (VMH), as well as single-cell recordings were used to study the interaction between IFN and glucose-sensitive neurons. IFN suppressed the majority (78%) of LH neurons, while reduction in glucose concentration elicited excitation in the majority (85%) of the same neurons. The opposite effects were observed in the VMH, where IFN excited the majority of neurons (61%), and reduction in glucose concentration exerted the opposite effects in 64% of VMH recordings. Concomitant IFN and glucose reduction exhibited only the effects elicited by IFN, regardless of whether the glucose reduction caused excitation (LH) or suppression (VMH). This observation suggests that IFN causes anorexia by modulating the LH and VMH glucose-sensitive neurons.

Key words Lateral hypothalamus · Ventromedial hypothalamus · Interferon · Glucose · Single cell · Ra

Introduction

Patients treated with interferon alpha (IFN) exhibit anorexia, which results in loss of more than 15% of their body weight (Adams et al. 1984; Bocci 1988; Meyers and Valentine 1995; Rohatiner et al. 1985). Anorexia is a serious, sometimes life-threatening disorder. The most conspicuous symptoms of this disorder are self-induced starvation and accompanying severe weight loss. A similar decrease in food intake following IFN administration has been obtained from animals (Crnic and Segal 1992; Plata-Salaman 1989; Reyes-Vazquez et al. 1994; Saphier et al. 1988; Segal and Crnic 1990). It has long been known that bilateral electrolytic lesion of the lateral hypothalamus (LH) area results in aphagia (cessation of eating; Anand and Brobeck 1951), which resembles anorexia. Both lesioning and complete deafferation of the ventromedial hypothalamus (VMH) elicit hyperphagia, which resembles obesity (Dafny et al. 1988; Rietveld et al. 1978). It is well known that the major central nervous system (CNS) areas participating in food intake control are thought to be the LH, the paraventricular nucleus (PVN), and the VMH (Dafny and Jacobson 1975; Dafny et al. 1988; Oomura 1988; Schanzer et al. 1978; Tempel et al. 1993). The LH was proposed to be "a center involved in initiating feeding" and the VMH to be responsible for producing the sensation of fullness, i.e., "a satiety center" (Hori et al. 1991; Morley 1987; Oomura 1988; Schanzer et al. 1978). These sites are also known to contain neurons that sense endogenous metabolic products such as glucose and engage in the control of food intake and energy balance (Luiten et al. 1987; Ono et al. 1980; Oomura 1988; Tempel et al. 1993). Therefore, in the present study, LH and VMH glucose-sensitive neurons were studied before and after IFN administration in coronal slices of rat brains to substantiate the role of IFN eliciting anorexia.

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Materials and methods

Coronal sections (350–400 μm thick) of the hypothalamus containing both the VMH and the LH area were sliced from brains of Wistar rats (100–200 g mass) using a Vibratome (Campden Instruments). The sections were incubated at 37°C for 1 h in a circulating, oxygenated artificial cerebrospinal fluid (ACSF). The bathing solution contained: 126 mM NaCl, 2.5 mM KCl, 1.24 mM NaH_2PO_4, 2.4 mM $CaCl_2$, 1.3 mM $MgCl_2$, and 26 mM $NaHCO_3$. The solution was saturated with 10 mM D-glucose, 95% O_2, 5% CO_2; pH 7.4 ± 0.1 and 300 msmol). For extracellular recording, the slices were transferred to a recording chamber (2.5 ml),

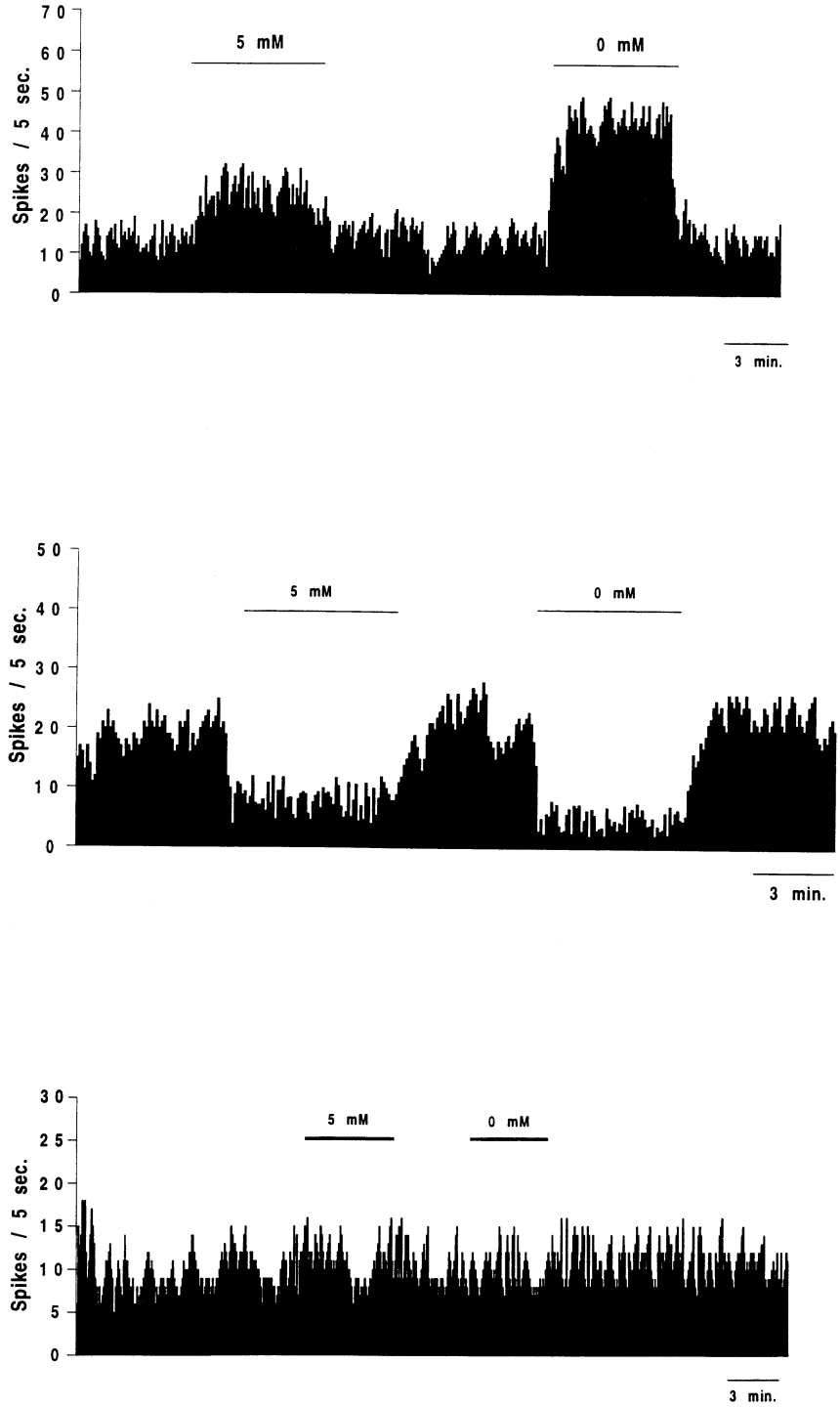

Fig. 1 Rate meters (frequency histograms) from lateral hypothalamus (LH) neurons following alteration of glucose concentration from 10 mM D-glucose to 5 mM and 0 mM, respectively. The LH and ventromedial hypothalamus exhibit three types of responses: excitation, type I (*upper histogram*); reduction in neuronal activity, type II (*middle histogram*); and unresponsive neurons following glucose alteration, type III (*lower histogram*)

where they were perfused with ACSF at 37°C, flowing at a rate of 4 ml min^{-1}. During the experiment, the bath content was modified by lowering the glucose concentration from 10 to 5 mM and to 0 mM; the osmolality of such solutions was adjusted to 300 msmol/kg by addition of sucrose and by changing the sodium concentration.

Extracellular single-neuron activities of VMH or LH neurons were recorded with a glass microelectrode (WPI) filled with fast green in 4 M NaCl (tips 1–3 μm, and ohmic impedance 10–30 MΩ). The recording electrode was placed in a micromanipulator and positioned over the section so that it was in contact with the surface of the tissue. A Narishige MO-8 hydraulic microdrive was used to further advance the electrode through the tissue under direct microscopic observation. The signal picked up by the recording electrode was amplified, filtered (bandpass 30–2000 Hz), and displayed on a Tektronix oscilloscope. A personal computer was used to process the spike activity and calculated the mean firing rate (spikes/second), store the data, and produce a frequency histogram (rate meter). The output was plotted on a chart recorder along with the section temperature.

The responsiveness of hypothalamic neurons to reduce in glucose concentration was studied by a 5-min perfusion of 5 mM and/or 0 mM D-glucose. Only those neurons that modified their frequency of discharge more than 40% as a result of glucose re-

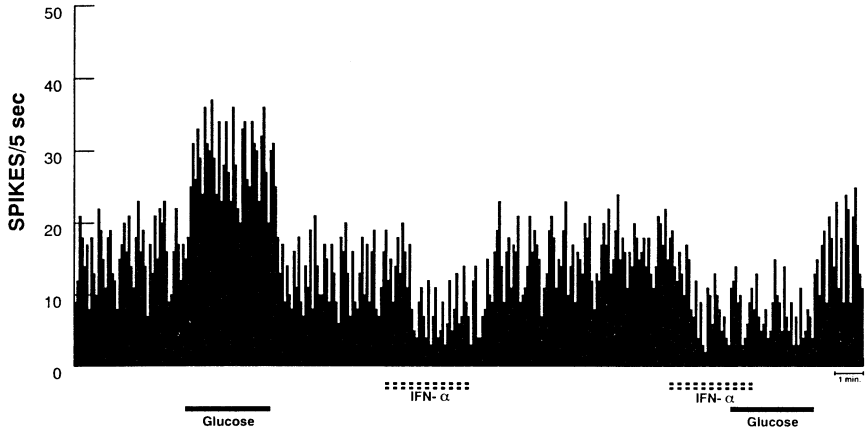

Fig. 2 Frequency histograms from representative LH neurons following glucose alteration to 5 mM D-glucose and following 1500 IU interferon-α (IFN-α) applied separately and together

Table 1 Responsiveness of lateral hypothalamus (*LH*) and ventromedial hypothalamus (*VMH*) units to reduction in glucose concentration and interferon-α (*IFN*) treatment. Values are the number of cells and their percentages (in parentheses) from the total number of neurons tested (*N*)

	Glucose		IFN		
	Responsive	Unresponsive	Responsive	Unresponsive	*N*
LH	39 (67%)	19 (33%)	38 (66%)	20 (34%)	58
VMH	41 (65%)	22 (35%)	31 (49%)	32 (51%)	63

Table 2 Under N are the total responsive neurons and how many of them (in percentage) were increased or decreased in their neuronal activity following reduction in glucose concentration or IFN treatment

	LH			VMH		
	N	Increase	Decrease	*N*	Increase	Decrease
Glucose	39	33(85%)	6 (15%)	41	15 (36)%	26 (64%)
IFN	38	9 (24%)	29 (76%)	31	19 (61)%	12 (39%)

duction were considered responsive to glucose, i.e., glucose-sensitive neuron (Dafny et al. 1985; Reyes-Vazquez et al. 1994).

Neuronal activity was studied also during application of 1000–1500 IUml of recombinant human IFN (activity 50 × 106 IU mg protein) given alone and together with 10 mM glucose solution. All solutions were introduced by an infusion pump (WPI PV800) into the immediate vicinity of the hypothalamic site for 5 min. After the recording session, an anodic current was passed through the microelectrode to deposit the fast green and mark the recording site.

Results

Effects of glucose

One hundred and twenty-one neurons were studied, 58 from the LH and 63 from the VMH. Recordings were obtained from 73 brain sections. Because the number of cells responding to 5 mM or 0 mM glucose and the degree and pattern of the cells firing rate were similar, the data were combined to one group for analysis. All of the recording neurons exhibited a single spike discharge with frequency ranges of 1.6–6.8 spikes/s (mean 2.6 ± 1.6 spikes/s) for the LH, and 0.9–8.6 spikes/s (mean 3.1 ± 1.6 spikes/s) for the VMH. The LH and VMH electrical activity of these 121 neurons were steady during the entire recording period, and no changes in spike pattern and/or spike size were observed before and after glucose or IFN treatment.

Neurons were classified into three main types according to their responses to decreases in glucose concentration. If their frequency of discharge increased, decreased, or stayed the same, type I neurons increased their frequency discharge (Fig. 1, upper histogram), type II neurons decreased their firing rate (Fig. 1, middle histogram), and type III neurons did not modify their response at all (Fig. 1, lower histogram). Of the 121 neurons recorded in both sites, a total of 80 (66%) units showed significant changes (type I or type II) in their firing rate after a decrease in glucose concentration. From 58 units recorded in the LH area, 39 (67%) were affected by a decrease in glucose concentration (Table 1). From these 39 LH responsive neurons, 33 (85%) increased their electrical activity following a decrease in glucose (Fig. 2) concentration (type 1 neurons), while only six units (15%) exhibited a decrease in their firing rates (type II) following a decrease in glucose concentration (Table 2).

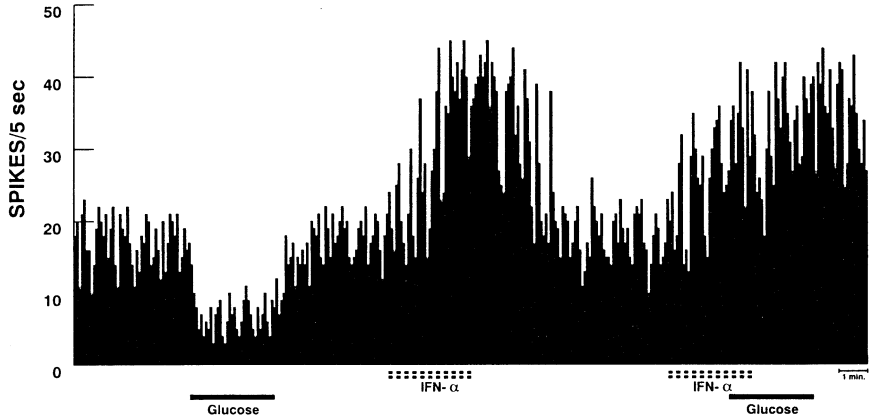

Fig. 3 Frequency histograms from representative ventromedial hypothalamus neurons following glucose alteration to 5 mM D-glucose and following 1500 IU IFN applied separately and together

Table 3 Summary of the number of LH and VMH neurons and their percentage responses to a decrease in glucose concentration by an increase (↑) or decrease (↓) in firing rates (*A*). Those units that failed to respond to a decrease in glucose concentration when IFN was given concomitant with glucose reduction, i.e., IFN prevented the glucose effect (*B*)

	LH		VMH	
	↑	↓	↑	↓
A	33 (100%)	6 (100%)	15 (100%)	26 (100%)
B	29 (88%)	1 (17%)	3 (33%)	19 (73%)

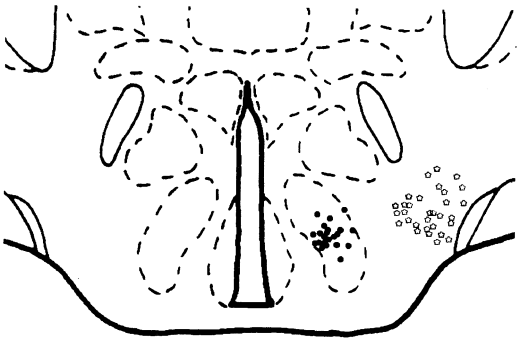

Fig. 4 Stereotaxic plates showing the reconstructed positions from histological material of the ventromedial hypothalamus (*black circles*) and LH (*open circles*) recording electrode tips

From the 63 units recorded in VMH, 41 (65%) responded to a decrease in glucose concentration. However, only 15 units (36%) showed an increase in their electrical activity after the decrease in glucose (Fig. 3) concentration (type I), and in 26 units (64%) the same glucose concentration (5 mM and/or 0 mM) elicited a decrease in their electrical activity (type II), in contrast to the observation obtained from the LH neurons. The remaining 22 units (35%) were unresponsive to glucose modification (type III; Table 2).

Most of the increased and decreased activity following a decrease in glucose concentration started 3–10 s after the infusion began, the effect lasted for 20–45 s postinfusion. There were no changes in the pattern or duration of the action potentials as a result of changing the glucose concentration.

Effect of interferon-α

The same 121 neurons were further investigated for their responsiveness to local perfusion of IFN (1000 –1500 IU/ml). From the 58 LH units recorded, 38 (66%) showed significant change after IFN infusion as compared to the control recordings, while only 31 of the VMH neurons (49%) were responsive to this cytokine (Table 1).

The most frequently observed effect following IFN treatment on LH neurons was a decrease in neuronal electrical activity (Fig. 2) as compared to their spontaneous activity (76%). Contrarily, the most frequently observed effect of IFN treatment in the VMH was an increase (Fig. 3) in their electrical discharges (61%), i.e., the opposite effect obtained from the LH units treated with IFN (Table 2).

Comparisons between the effects of IFN and glucose on LH and VMH neurons

Twenty-five (77%) out of the 33 LH neurons excited by a decrease in glucose concentration were depressed by IFN, while 21 (81%) out of 26 VMH glucose-depressed units were excited by the infusion of IFN. In both the LH and VMH sites, the onset latencies of the excitation and the inhibition responses elicited by IFN were 69 ± 6.7 and 94 ± 16.3 s, respectively. After switching off the IFN administration, the excitation responses continued for an additional 124 ± 32.5 s; and the inhibition effects, for an additional 197 ± 56.2 s. Only three non-glucose-sensitive units (one from LH and two from the VMH) responded to IFN infusion.

Effects of concomitant glucose reduction and IFN

Finally, the effects of IFN concomitant with reduction in glucose concentration were investigated. In the LH, IFN

blocked the excitatory response elicited by glucose reduction in 29 out of the 33 affected cells (88%) (Fig. 2) and reversed the glucose reduction-induced depressed effects on one cell. However, in VMH the depressing action elicited by glucose reduction was prevented in 19 cells out of the 26 affected neurons (73%; Fig. 3) and the excitatory action was blocked in three cells by the infusion of IFN (Table 3).

In the VMH, most of the glucose and IFN affected cells were localized in the middle of the nuclei in a very narrow region; contrarily in the lateral hypothalamus, the distribution of these units was wider (Fig. 4).

Discussion

The hypothalamus is one of the CNS areas involved in the integration of metabolic, neural, and humoral signals resulting in the regulation of the metabolism (Blundell 1991; Niijima 1989; Rowe et al. 1996). Electrophysiological studies have shown that IFN-induced feeding suppression might involve excitation of glucose-sensitive neurons in the VMH (Nakashima et al. 1987; Oomura 1988) and decreased activity in glucose-sensitive LH neurons. Glucose-induced excitation of rat hypothalamic neurons was reported (Ashford et. al. 1990; Rowe et al. 1996) and suggested to be mediated by ATP-sensitive K^+ channels. Similar observations have been reported in other electrophysiological studies, which show that cytokines such as interleukin-1 (IL-1) and tumor necrosis factor (TNF), for example, elicited feeding suppression and engaged in the inhibited glucose-sensitive neurons in the LH (area considered to be a ”hunger center”). The feeding pattern induced by various immunoregulators was consistent with the decrease in activity of LH neurons (Kow and Pfaff 1985; Plata-Salaman 1991). Two-thirds of glucose-sensitive VMH neurons responded to both IFN and IL-1. Increases in firing rate were observed in the majority of the VMH neurons, while suppression of firing rate was obtained in the majority of LH neurons (Hori et al. 1991; Plata-Salaman et al. 1988). The response of glucose-sensitive cells in the VMH to local application of IFN might explain cytokine-induced anorexia (Hori et. al. 1991).

The main finding of this study is that the majority of LH neurons were excited following reduction of glucose concentration, while the majority of the glucose-sensitive VMH neurons were suppressed. In the LH and VMH, IFN in a dose considered to be physiological (Gutterman 1994), elicits the opposite effects from those obtained following glucose alteration: the majority of the LH neurons were suppressed, while the majority of the VMH neurons were excited following IFN administration. Moreover, when IFN and glucose reduction were administered together, IFN prevented the glucose reduction-induced effects in both the LH and VMH sites, whether the glucose reduction caused excitation, i.e., in the LH, or whether the glucose reduction cause suppression, i.e., in the VMH.

In previous experiments using microiontophoretic application of IFN on VMH neurons (Dafny et al. 1985; Prieto-Gomez et al. 1983), excitation was observed, while the opposite effects were obtained from LH neurons (Reyes-Vazquez et al. 1994). Similarly, contrary observations between LH and VMH, induced by morphine, were reported by Kerr et al. (1974). The reciprocal interaction between LH and VMH in mechanisms of hunger and satiety have been documented extensively (Schanzer et al. 1978; Dafny et al. 1988). Therefore, it is possible that IFN affects both VMH and LH in a reciprocal (push-pull) manner in regulating food intake. Additionally, when concomitant IFN and glucose reduction were given, the IFN prevented the glucose reduction from eliciting excitation in the LH and attenuation in the VMH. Therefore, it is possible to conclude that IFN modulates both the LH and the VMH to regulate feeding behavior. This agrees with the suggestion of Hori et al. (1991) that cytokine-induced suppression of food intake involves the excitation of glucose-sensitive excitatory neurons in the VMH and the inhibition of glucose-sensitive neurons in the LH.

In healthy subjects, plasma IFN levels early in the day (at 0600 hours) are negligible, but increase during the day to a peak level at 1800 hours. Furthermore, it has been shown that there is a significant increase in IFN plasma levels 2 h after meals. This IFN peak is transient and falls rapidly back to baseline levels (Bocci et al. 1985). These results suggest that IFN is involved in feeding regulation.

Several mechanisms other than the actions of cytokine on glucose-responsive neurons have been suggested for cytokine-induced anorexia. Although cytokines are known to suppress food intake independently of fever, the body temperature increase itself might inhibit feeding by directly modulating the activity of glucose-responsive neurons in the VMH and LH (Hori et al. 1988; Nakayama et al. 1981). Evidence has been provided that immunoregulators such as ILs and IFN induce sleep (Birmanns et al. 1990; Dafny 1983; DeSarro et al. 1990; Krueger et al. 1987; Plata-Salaman 1991; Saphier et al. 1987, 1988). Sleep prevents eating, which will also result in weight loss (Paulesu et al. 1985). IFN elicits excitatory effects on some glucose-sensitive neurons that are excited by morphine (Reyes-Vazquez et al. 1994) and by endogenous opioid peptides (Ono et al. 1980). Furthermore, excitatory neuronal responses to direct perfusion on brain tissue slices of IFN in the VMH, recorded from glucose-sensitive neurons, are also antagonized by naloxone (Nakashima et al. 1987 1988). It has been suggested that these responses are directly related to the loss of appetite observed during IFN therapy (Meyers et al. 1991). Direct interaction of IFN with opioid receptors is a plausible explanation for the observed effects on temperature and glucose-sensitive neurons (Nakashima et al. 1987 1988; Kuriyama et al. 1990). Thus, the mechanisms by which cytokines induce anorexia are considered to be multifactorial (Hori et al. 1991).

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