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CHAPTER 22

Hypothalamic integration of immune function and metabolism

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Abstract: The immune and neuroendocrine systems are closely involved in the regulation of metabolism at peripheral and central hypothalamic levels. In both physiological (meals) and pathological (infections, traumas and tumors) conditions immune cells are activated responding with the release of cytokines and other immune mediators (afferent signals). In the hypothalamus (central integration), cytokines influence metabolism by acting on nucleus involved in feeding and homeostasis regulation leading to the acute phase response (efferent signals) aimed to maintain the body integrity.

Peripheral administration of cytokines, inoculation of tumor and induction of infection alter, by means of cytokine action, the normal pattern of food intake affecting meal size and meal number suggesting that cytokines acted differentially on specific hypothalamic neurons. The effect of cytokines-related cancer anorexia is also exerted peripherally. Increase plasma concentrations of insulin and free tryptophan and decrease gastric emptying and D-xylose absorption. In addition, in obesity an increase in interleukin (IL)-1 and IL-6 occurs in mesenteric fat tissue, which together with an increase in corticosterone, is associated with hyperglycemia, dyslipidemias and insulin resistance of obesity-related metabolic syndrome. These changes in circulating nutrients and hormones are sensed by hypothalamic neurons that influence food intake and metabolism.

In anorectic tumor-bearing rats, we detected upregulation of IL-1β and IL-1 receptor mRNA levels in the hypothalamus, a negative correlation between IL-1 concentration in cerebro-spinal fluid and food intake and high levels of hypothalamic serotonin, and these differences disappeared after tumor removal. Moreover, there is an interaction between serotonin and IL-1 in the development of cancer anorexia as well as an increase in hypothalamic dopamine and serotonin production. Immunohistochemical studies have shown a decrease in neuropeptide Y (NPY) and dopamine (DA) and an increase in serotonin concentration in tumor-bearing rats, in first- and second-order hypothalamic nuclei, while tumor resection reverted these changes and normalized food intake, suggesting negative regulation of NPY and DA systems by cytokines during anorexia, probably mediated by serotonin that appears to play a pivotal role in the regulation of food intake in cancer.

Among the different forms of therapy, nutritional manipulation of diet in tumor-bearing state has been investigated. Supplementation of tumor bearing rats with ω-3 fatty acid vs. control diet delayed the appearance of tumor, reduced tumor-growth rate and volume, negated onset of anorexia,

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increased body weight, decreased cytokines production and increased expression of NPY and decreased α-melanocyte-stimulating hormone (α-MSH) in hypothalamic nuclei. These data suggest that ω-3 fatty acid suppressed pro-inflammatory cytokines production and improved food intake by normalizing hypothalamic food intake-related peptides and point to the possibility of a therapeutic use of these fatty acids.

The sum of these data support the concept that immune cell-derived cytokines are closely related with the regulation of metabolism and have both central and peripheral actions, inducing anorexia via hypothalamic anorectic factors, including serotonin and dopamine, and inhibiting NPY leading to a reduction in food intake and body weight, emphasizing the interconnection of the immune and neuroendocrine systems in regulating metabolism during infectious process, cachexia and obesity.

Introduction

The quote an ''An army marches on its stomach,'' often attributed to Napoleon, links the rallying of bodily defenses with the appropriate marshalling of nutrient responses. In this analogy General Baron De Jomini (Fig. 1), Napoleon's Quartermaster, represents the ''hypothalamus'' which plays an important role in defining the magnitude and temporal profile of hypothalamic nuclei responses by integrating these with the responses from the rest of the brain (central events) and initiating hormonal release by the hypothalamic–pituitary–adrenal axis (HPA). He assessed the magnitude and type of the danger encountered by Napoleon's troops in a battle (afferent signals) and ensured the army had appropriate supplies to react in a timely fashion and to behave by a measured response (efferent signals) to overcome the immediate threat. Like any good army, communication pathways exist between the immune system and the brain allowing bi-directional regulation of the immune- and the brain-initiated behavioral responses, thereby maintaining homeostatic regulation of the body and stability of the army.

Fig. 1. General Baron De Jomini.

Napoleon and De Jomini were less successful when it came to long-term campaigns under adverse conditions as reflected by the retreat from Moscow. So too the hypothalamus reacts to a foreign stimulus by mounting an acute phase response via modulating the neuroendocrine system and through the HPA axis to altered peripheral metabolism of carbohydrates, proteins and fats to ensure an immediate energy-rich milieu to sustain immune function, while optimally conserving long-term body energy status. However, like Napoleon's long-term campaign, the acute phase response is ill suited for protracted immune challenges, such as morbid obesity or Crohn's disease, which result in chronic and life-threatening conditions.

The term *acute phase response* refers to the inflammatory response of the host occurring shortly after any tissue injury. The purpose of the acute phase response is to prevent further injury of an organ, to limit the growth of the infective organism, to remove harmful molecules and to activate the repair processes to return the organ to normal function. The acute phase response is characterized by the systemic inflammatory signs of fever, anorexia,

somnolence and depression, which are a reflection of the integration of multiple neuro-endocrine, immunological, metabolic and neurological changes in response to the afferent stimulus. The intensity of the acute phase response varies with the acute stimulus and when it becomes overwhelming conditions, such as ileitis or obesity produce profound morphologic and metabolic changes that induce chronic illness and impair survival.

The transmission of the peripheral immune information to the brain is carried out by two different pathways: (i) blood-borne mechanisms: cytokines reach the brain by crossing blood–brain barrier via active transport (Banks et al., 1991), by means of circumventricular organs, such as vascular organ of the lamina terminalis, median eminence and area postrema (which lack a blood–-brain barrier so that fenestrated capillaries allow plasma passage; Blatteis, 1992) or by binding to cerebral blood vessel endothelium leading to the release of other second messengers such as prostaglandins (Ericsson et al., 1997). (ii) By means of the vagus nerve (Goehler et al., 1997, 1999, 2000; Ek et al., 1998; Mascarucci et al., 1998; Hosoi et al., 2000). Stimulation of vagus nerve by pathogens or immune cells-derived mediators is followed by the activation of neurons in the nucleus tractus solitarius (Konsman et al., 2000), which send projections to hypothalamic and limbic areas involved in regulation of feeding behavior (Ricardo and Koh, 1978). In the vagally mediated immunosignal to the brain, dendritic cells play an important role given its prominent localization within the vagus nerve and associated paraganglia (Goehler et al., 1999). Apart from the direct stimulation of vagal afferents by immune cell-derived mediators, these signals can activate chemoreceptive cells located in the vagal paraganglia, which are penetrated by blood and lymph vessels, allowing vagal paraganglia to sense compounds circulating in blood or lymph (Goehler et al., 2000).

Afferent signals and central events-behavioral and physiological components

A number of examples are sighted below to demonstrate our understanding of the common features of the acute response and function of the afferent signal mechanism(s) that impinge on central event, initiating the acute phase response as manifested by changes in behavior using food intake, and its components (meal size and meal number) as a biological index. To illustrate these points we will use data based on our work and augment it with data from the literature.

Responses to oral food

Ingested nutrients are strong macromolecular antigens that actively challenge the gut's immune defense mechanism. These consist of intestinal lymphoid cells that secrete intraluminal immunoglobulins and local cytokines that (i) further recruit immune cells from the circulation to the gut lymphoid tissue, and (ii) simultaneously mount a systemic acute phase immune response, mediated via afferent blood-borne and neuroendocrine pathways to the liver and ultimately to the hypothalamus. Hansen et al. examined the effect of a single high-protein meal on peripheral immune response by measuring blood mononuclear cells, plasma concentrations of tumor necrosis factor-α (TNF-α), IL-6 and cortisol and growth hormone (Hansen et al., 1997). After the 30 min meal (Fig. 2A) a significant rise of peripheral neutrophils within 15 min of completing the meal occurred and which remained elevated for 3.5 h. At the same time, a significant decrease in circulating lymphocytes occurred accompanied by a sharp rise in cortisol that started to increase during the meal and peaked shortly thereafter (Fig. 2B). An increase in plasma cytokines levels was not detected. In a follow up "cafeteria-diet" paradigm rat study, an increase in IL-1β mRNA expression occurred in liver and hypothalamus, while an associated decrease in IL-1 receptor accessory proteins (IL-1RAP) mRNA (reflecting IL-1's binding and signaling capacity) occurred in liver and brain stem (Hansen et al., 1998).

Both studies present interesting results. The intrameal rise in cortisol indicates that afferent signals, such as nutrients or hormones, rapidly reached the hypothalamus, particularly the arcuate nucleus (ARC), probably via blood-borne afferent stimuli through the median eminence and via gastrointestinal vagal afferents. The ARC projects to

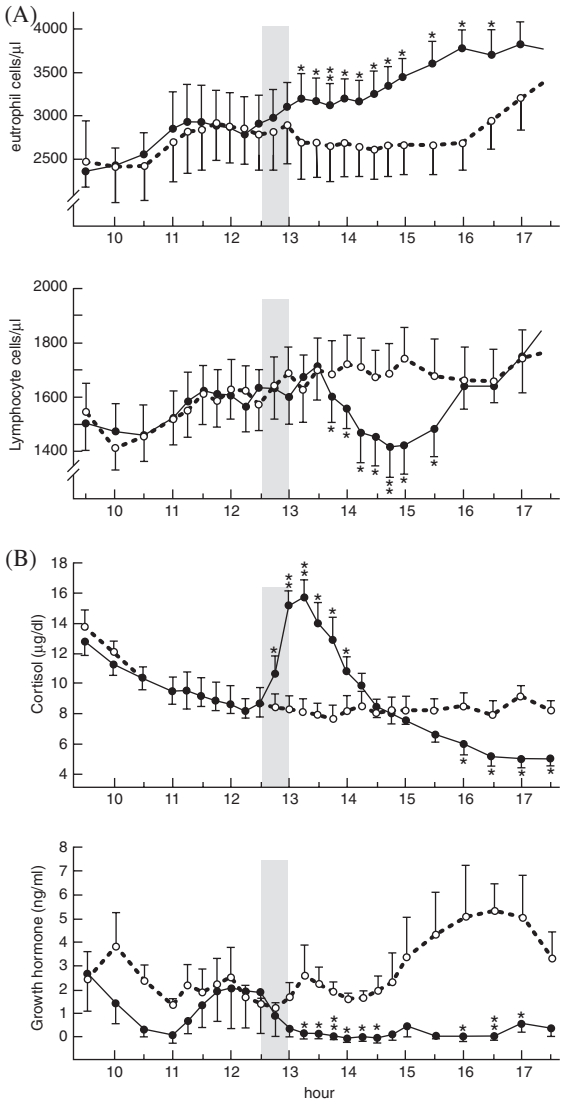

Fig. 2. Effect of a single high-protein meal on peripheral immune response. (A) After the 30 min meal a significant rise of neutrophils within 15 min of completing the meal occurred and which remained elevated for 3.5 h. (B) At the same time, a significant decrease in circulating lymphocytes occurred accompanied by a sharp rise in cortisol that started to increase during the meal and peaked shortly thereafter. (From Hansen et al., 1997).

the paraventricular nucleus (PVN) which releases corticotropin-releasing factor (CRF) into the portal plexus at the median eminence eliciting the synthesis and release of adrenocorticotropin hormone (ACTH) from the anterior pituitary that stimulated the adrenal gland to secrete cortisol, which influenced the migration of immune cell from the circulation into extra-vascular gut tissue to support local immune function (Ottaway and Husband, 1994). The increase in IL-1β mRNA in the hypothalamus and the decrease in IL-1RAP mRNA in brain stem confirms the role of the vagal visceral chemosensory pathway as one of the routes for afferent signals from the gastrointestinal tract to hypothalamic nuclei via the dorsomotor vagal complex of the medulla. Despite Hansen et al.'s inability to detect cytokines in the circulation in response to the *physiological* event of a single meal, in a *pathological* model of shock-induced intestinal injury, Deitch et al. demonstrated that the gut liberates cytokines (Deitch et al., 1994). Concentrations of IL-6 and TNF were significantly higher in portal blood than cardiac blood.

In response to the increased intraportal IL-1β, Niijima (1996) demonstrated an increased vagal afferent electrical activity in a dose-dependent response with a simultaneous decreased efferent sympathetic splanchnic activity and a simultaneous increase in vagal thymic nerve activity (see section on Efferent signals). Similar findings were reported by Niijima and Meguid in response to intraportal arginine, an amino acid known to enhance immunity (Niijima and Meguid, 1998) by stimulating increased T-cell release from the thymus and inhibiting the spleen from taking up circulating lymphocytes. The net result is to enhance the circulating numbers and phagocytical active T and B cells (Fig. 3).

Responses to continuous intravenous nutrients

In a parallel series of studies we continuously infused graded caloric amounts of intravenous nutrients for 3 or 9 days (total parenteral nutrition) into the rat, while measuring the response of oral food intake, meal patterns, peripheral hormones, cytokines, hepatic vagal afferent activity and intrahypothalamic monoamines (Opara et al., 1996). Figure 4 shows that graded amounts of total parenteral nutrition lead to a graded compensatory decrease in oral intake. The graded compensatory decrease in oral intake persisted for the duration of the infusion. Plasma glucose

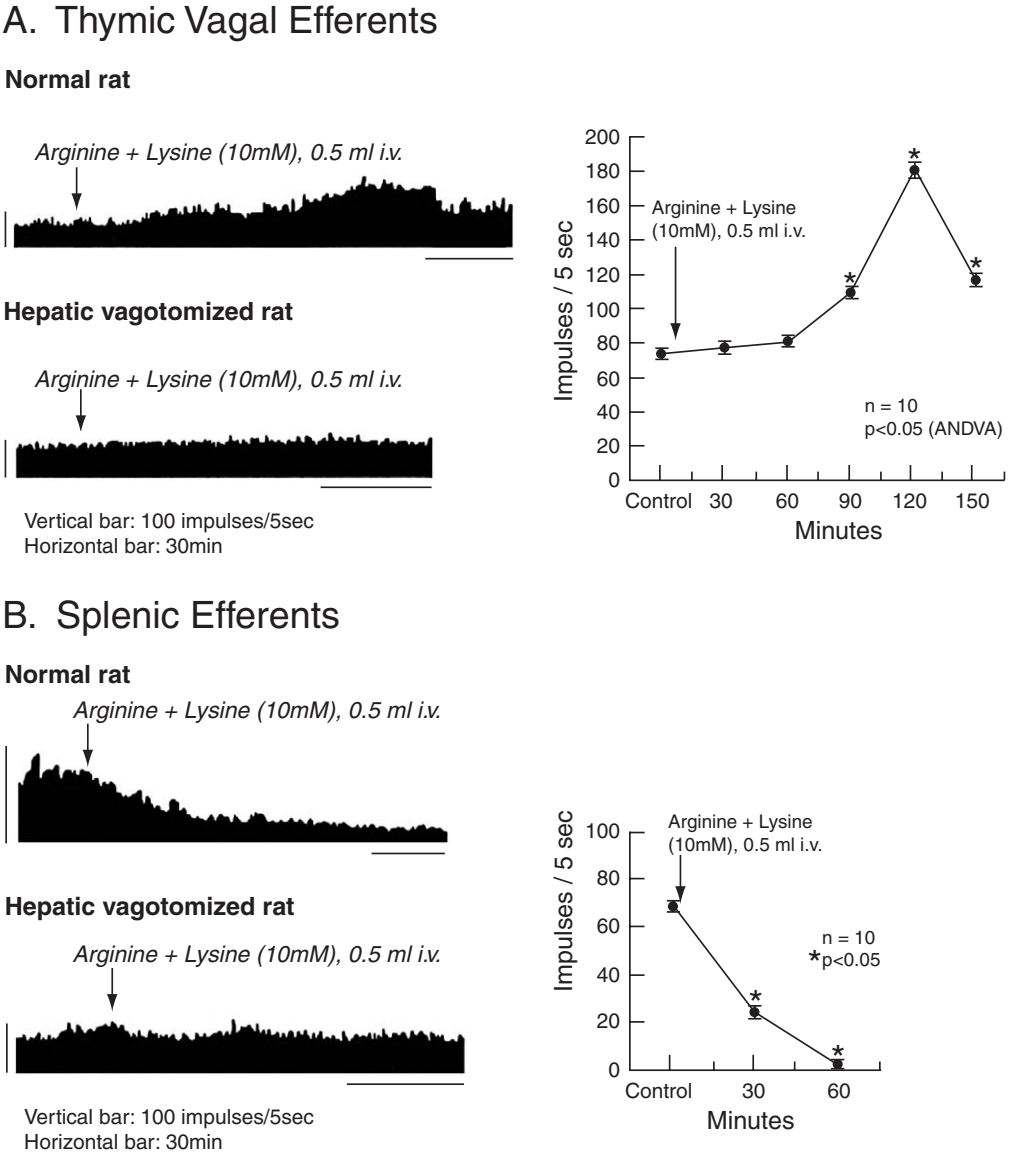

Fig. 3. Effect of intravenous administration of a mixture solution of Arg and Lys (10 mM, 0.5 ml) on the efferent activity of the (A) thymic branch of the vagus nerve and (B) the efferent activity of the splenic nerve in normal and hepatic vagotomized rats. $*p<0.05$. (From Niijima and Meguid, 1998).

and insulin significantly increase and whereas hepatic glycogen concentrations decreased, hepatic triglyceride concentrations significantly increased (Meguid et al., 1991). Simultaneously, plasma TNF-α and peripheral blood monocyte IL-1 also significantly increased (Opara et al., 1995b), while intraportal nutrients decreased hepatic vagal firing rates (Niijima and Meguid, 1994). Interestingly, the response of the hepatic vagal afferent firing rate varied according to the type of amino acid infused intraportally. Thus, of 15 different amino acids infused intraportally (10 mmol in 0.1 ml), eight were excitatory and increased the vagal afferent firing rate, while the others were inhibitory and

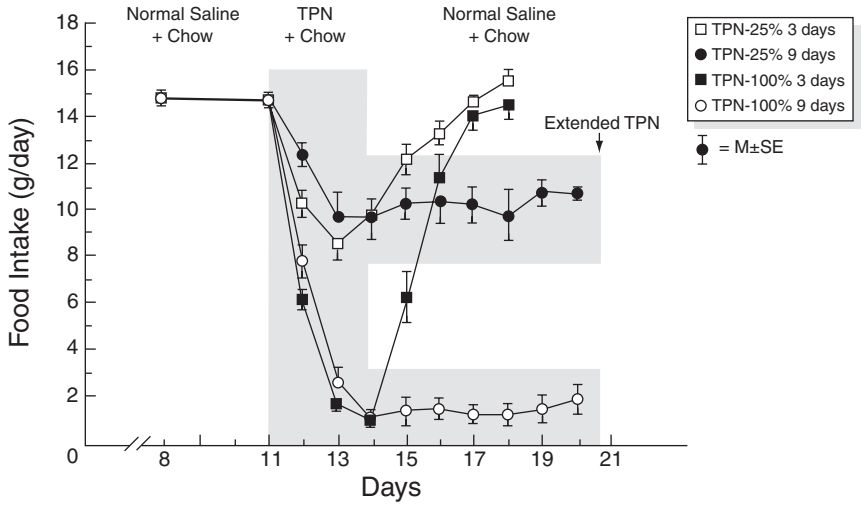

Fig. 4. Spontaneous food intake in rats receiving total parenteral nutrition (TPN-25 or TPN-100) for 3 or 9 days. TPN-25 indicates the amount of total parenteral nutrition that provides 25% of a rat's daily caloric intake; TPN-100, the amount of total parenteral nutrition that provides 100% of the rat's daily caloric intake. Values are the mean ± SEM. Total parenteral nutrition decreased spontaneous food intake in proportion to the amount infused. (From Campos et al., 1990).

decreased the firing rate. The change in afferent activity to the hypothalamus may affect reflex regulation of the visceral functions and thereby influence appetite (Niijima and Meguid, 1995). Intralateral hypothalamic area (LHA) neuron dopaminergic activity in response to total parenteral nutrition or its constituent's nutrients was measured by microdialysis (Meguid et al., 1993). LHA-DA levels rose and remained elevated during a continuous 3-h peripheral total parenteral nutrition infusion. Similar increases in LHA-DA occurred during peripheral glucose, fat and amino acid infusion. However, after cessation of these peripherally infused solutions, glucose was the only solution where the percent of DA decrease below baseline for 3 h. A similar relationship was determined between LHA-DA to oral intake in normal rats. The ingestion of a single meal induced a rise in LHA-DA, as measured via microdialysis, that was double in magnitude to that induced by to a meal one-half the size (Meguid et al., 1995). A reciprocal relationship exists between the LHA and ventromedial hypothalamus (VMH) in food intake regulation. Thus, the relationship of DA to the VMH was also explored. DA-VMH concentrations decreased during eating, and the degree and duration of decrease after the meal corresponded to the size of the meal. When the decreased postmeal VMH-DA level had returned to baseline, rats ate once more. We infer from the data that in normal rats eating was associated with decreased DA levels in the VMH, that was followed by a lag time during which no additional eating occurred suggesting that VMH-DA levels contributed to determining the duration of the intermeal interval and hence by influence meal frequency (Meguid et al., 1997).

These studies present two striking results. First, the increased circulating nutrients and insulin led to a form of anorexia by compensating for the increased caloric intake. Second, the stress of the continuous hypertonic infusion increased TNF-α and IL-1 contributing to the cytokine mechanism that decreases oral intake in the rat. The ARC, which is the nodal point in hypothalamic regulation of energy balance, promptly senses these nutrients. The leptin- and ghrelin-responsive ARC neurons affect the activity of neurons in PVN, VMH and LHA and other key effector central sites (Elias et al., 1998, 1999; Cowley et al., 1999; Saper et al., 2002), which contain orexigenic and anorexigenic neuropeptides, including orexin-A

and -B, cholecystokinine and melanin concentrating hormone (MCH). Many of these central sites are linked to the hypophysiothropic, behavioral and autonomic adaptive responses to changes in energy status (Zigman and Elmquist, 2003). The ARC project neurons to the LHA that plays a key role in ingestive behavior and energy balance, because of the neurochemical phenotypes of the cells express melanocortin hormones and orexin (see section on Central integration). These neurons also synthesize and release DA that "stimulate" or "inhibit" regulatory control over the HPA (Meguid et al., 1995). Thus, although the rise in LHA-DA in our study could have been anticipated, the fall in LHA-DA after the cessation of only the intravenous glucose, supports the concept of the glucose-sensing capacity of the neurons in the ARC, PVN and the LHA (Elmquist and Marcus, 2003). No such response occurred with cessation of the complex solutions that constitute total parenteral nutrition, fat emulsion or amino acid solution, all of which are compound solutions. These data indicate that blood-borne factors are sensed by the hypothalamus but particularly by the ARC and that this sensing mechanism constitutes part of the acute phase response system. At the same time, the increase in TNF-α and IL-1 was likely sensed by the brain via the afferent hepatic vagus because when a sub-diaphragmatic vagotomy was performed, vagotomized rats consumed more food during total parenteral nutrition. They did this by increasing the frequency, size and duration of a meal, suggesting that the influence of blood-borne nutrient and insulin on the ARC was greater than the effect that TNF-α had in decreasing food intake vial abdominal vagus (Yang et al., 1992; Opara et al., 1995b). Based on these results it appears that the cytokine response to the continuous infusion of hypertonic nutrients has a quantitatively greater inhibitory effect on food intake than the continuous nutrient supply.

Afferent signals from a peripheral tumor

Another model that we have used extensively in our laboratory to gain insight into the integrative acute phase response to peripheral signals is the methylcholanthrene sarcoma without inducing metastases in the rat model that induces anorexia as the tumor grows. When 10^6 methylcholanthrene-sarcoma tumor cells are injected into the flank of a Fischer rat a palpable tumor is detected after 10 days. The tumor's exponential growth results in a 1 cm^3 mass between 16 and 20 days (Meguid et al., 1987). During tumor growth, meal number gradually declines with time, but food intake is maintained by a compensatory increase in meal size between 18 and 20 days. When this compensation fails, food intake dramatically decreases and anorexia is behaviorally manifested. Interferon-γ (INF-γ) was detected in the tumor tissue, while we measured a significant increase in IL-1β and in IL-1 receptor 1 mRNA expression in the hypothalamus, cerebellum and hippocampus. Simultaneously, we detected an increase in IL-1RAP 1 and 2 in the liver confirming activity of IL-1 in the periphery (Fig. 5; Turrin et al., 2004).

These studies clearly indicate that the peripherally growing tumor is challenged by immune cells to elaborate both TNF-α and IL-1β. Yang et al. (1994) demonstrated that a 3-day infusion of subclinical concentrations of TNF-α and IL-1 induced anorexia via a synergistic effect, each having no biological effect when infused separately. These act not only on both the parvocellular and the magnocellular neuronal population of the PVN to modulate the acute phase response to induce anorexia thereby decreasing meal size and meal number, which are the components of food intake as measured by our Automated Computerized Rat Eater Meter (Meguid et al., 1990; Meguid et al., 1998); but also on other brain regions involved with locomotion to conserve energy and on memory to respond appropriately to the acute phase response event. Understanding the component of food intake i.e., whether it is meal number or/and meal size, decrease or change, is a useful behavioral index. It reflects where in the hypothalamus and on which neuron population afferent signals, such as cytokines, act. Using an injection of fetal serotonergic or dopaminergic cell suspensions into the LHA, VMN or supraoptic nucleus (SON) we demonstrated that either meal size or meal number or both could be manipulated, suggesting that these neurotransmitters had co-receptors on the primary neuropeptide food-regulating neurons (Meguid et al., 1999).

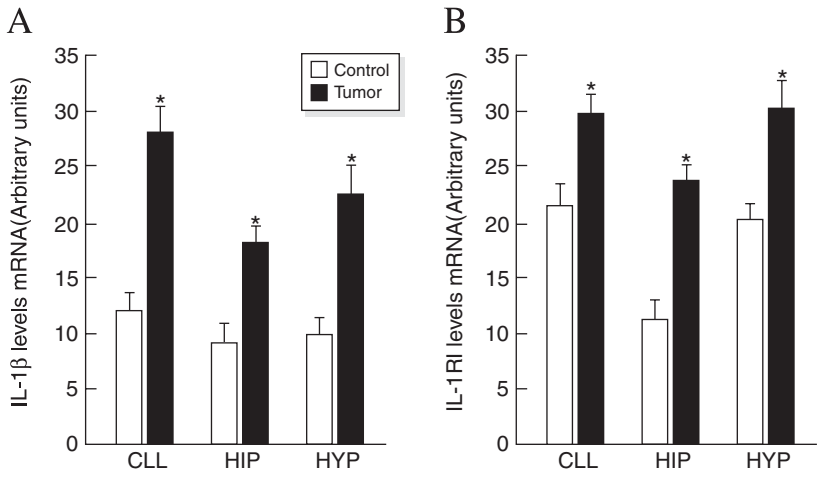

Fig. 5. (A) Increased expression of IL-1 β mRNA levels in cerebellum (CLL), hippocampus (Hip) and hypothalamus (Hyp) with peripheral tumor growth and (B) IL-1 RI mRNA levels in controls or tumor-bearing rats. Values (means ± SE; $n = 8$ for each group) were standardized to arbitrary units. *$p < 0.05$ vs. controls. (From Turrin et al., 2004).

Responses to a viral and bacterial infection

During an outbreak of a sialodacryoadenitis viral infection in our rat colony we detected that food intake markedly decreased when the rats become clinically symptomatic (Sato et al., 2001c). This reduction in food intake occurred via a decrease in meal size not adequately compensated by an increase in meal number that occurred during both the light and dark phase. This pattern is similar to that which we described in anorexia of indomethacin-induced ulcerative ileitis that is accompanied by an increase in plasma concentrations of TNF-α (Veerabagu et al., 1996), but differed from that observed in anorexia of bacterial lipopolysaccharide-induced infections (Langhans et al., 1991a; Porter et al., 1998) and in cancer anorexia (Meguid et al., 2000). Table 1 compares the different responses of both components of food intake to different stimuli.

The reduced food intake during sialodacryoadenitis infection, which is a corona virus, is probably due to TNF-α because corona viruses induce an increase in this cytokine (Itoh et al., 1991) and using anti-TNF-α agent inhibits TNF-α induced anorexia (Porter et al., 2000), while the participation of IL-1β seems to be limited given that even in IL-1β-deficient mice the anorexia induced by influenza virus is severe (Kozak et al., 1995). The effect of TNF-α on food intake may be partly mediated by changes in hypothalamic DA levels, because in a cecal ligation and puncture septic rat model studied in our laboratory, a progressive decrease in VMH-DA concentrations associated with anorexia was demonstrated (Torelli et al., 2000). Besides the role of TNF-α in sialodacryoadenitis-induced anorexia the participation of other factors, including IL-2, IL-6, IL-8 and/or INT-γ has been suggested (Conn et al., 1995; Plata-Salaman, 1996; Arsenijevic and Richard, 1999).

During bacterial infection IL1-β seems to play and important role in anorexia induction (Von Meyenburg et al., 2003). MohanKumar et al. (1999) found a marked increase in DA, norepinephrine (NE), serotonin (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) in PVN, as well as an increase in DA concentrations in ARC, two nuclei involved in the control of food intake, after lipopolysaccharide intraperitoneal administration. These changes are completely blocked by treatment with IL-1ra, suggesting the participation of IL-1β in these monoamine metabolism alterations, which is able to induce changes in neurotransmitters concentrations in specific hypothalamic areas (MohanKumar et al., 1998).

Table 1. Different responses of both components of food intake, meal number (MN) and meal size (MZ), to different stimuli

Stimuli	MN	MZ	Reference
TPN	↓	↓	Meguid et al. (1991)
MDP	↓	↔	Langhans et al. (1991a)
IL1-α	↓	↓	Debonis et al. (1995)
Ulcerative ileitis	↔	↓	Veerabagu et al. (1996)
LPS	↓	↔	Porter et al. (1998)
Tumor	↓	↓	Meguid et al. (2000)
SDA	↔	↓	Sato et al. (2001c)

Note: ↔ No change; ↓ decrease. LPS, lipopolysaccharide; MDP, muramyl dipeptide; TPN, total parenteral nutrition; SDA, sialodacryoadenitis.

Gonadal hormones and sexual dimorphic-based acute phase response

Another critical model studied in our laboratory that has profound influence on hypothalamic integration of immune function and metabolism is the sex of the study model given that gender differences exist in the acute phase response (Coe and Ross, 1983; Hirai and Limaos, 1990; Spitzer and Zhang, 1996a, b).

Although daily food intake based on 100 g-body weight is similar in males and females rats, during a 44-day observation period of weight-gain rate in young growing adults was sevenfold greater in males than in females, and the pattern of food intake differed between both sexes. Thus, while in males the constancy of food intake was achieved by an increase on meal size compensated by a decrease in meal number the striking observation in comparably aged female rats is that their food intake is relatively stable, because there are cyclical and reciprocally recurring changes in both meal size and meal number (Fig. 6), which are synchronized with the 3–4 days estrous cycle, such that meal number is greatest during estrous phase and meal size is small, while during the met-estrous cycle meal size is largest and meal number is the lowest (Laviano et al., 1996).

Estrogen modulates the neurons in suprachiasmatic nucleus (SCN, Hansen et al., 1978, 1979), the nucleus tractus solitarius (Eckel and Geary, 2001; Eckel et al., 2002), preoptic area (Dagnault and Richard, 1997), VMH (Beatty et al., 1974) and parvocellular division of PVN (Butera and Beikirch, 1989; Eckel and Geary, 2001; Eckel et al., 2002) to reduce food intake, which is not mediated by CRF (Dagnault and Richard, 1997) or by cholecystokinin (Flanagan-Cato et al., 1998; Eckel et al., 2002). In our studies, the role played by the gonadal hormones in this different behavior of food intake pattern was tested by ovariectomy, which resulted in a loss of cyclic feeding pattern, and an increase in daily food intake caused primarily by an increase in light phase meal size. This pattern of feeding behavior was reversed and normalized after exogenous estrogen restoration, resulting in body weight preservation (Varma et al., 1999). In contrast, orchiectomy reduced food intake by reduction of meal number. This pattern was normalized after exogenous testosterone was given, reversing weight loss (Chai et al., 1999). Our interpretation of the differences in the feeding pattern in females may be explained teleologically by the need to find a mate. Foraging for food during estrous exposes the female to maximum number of potential males, necessitating an increase in meal number but lower meal size, while during met-estrous, when the chances of mating are lowest the meal size are greatest. No such similar evolutionary need is necessary in male rats.

However, in the context of the acute phase response to a noxious stimulus, these data become important because the distribution of meals during the day and night are regulated by the circadian control of energy homeostasis. Thus the sex of the subject, which is receiving the insult, is critical in determining the response. In the female rat, energy regulation occurs primarily by changing meal size, not meal number. Estradiol acts directly on the SCN (Hansen et al., 1978, 1979) the main

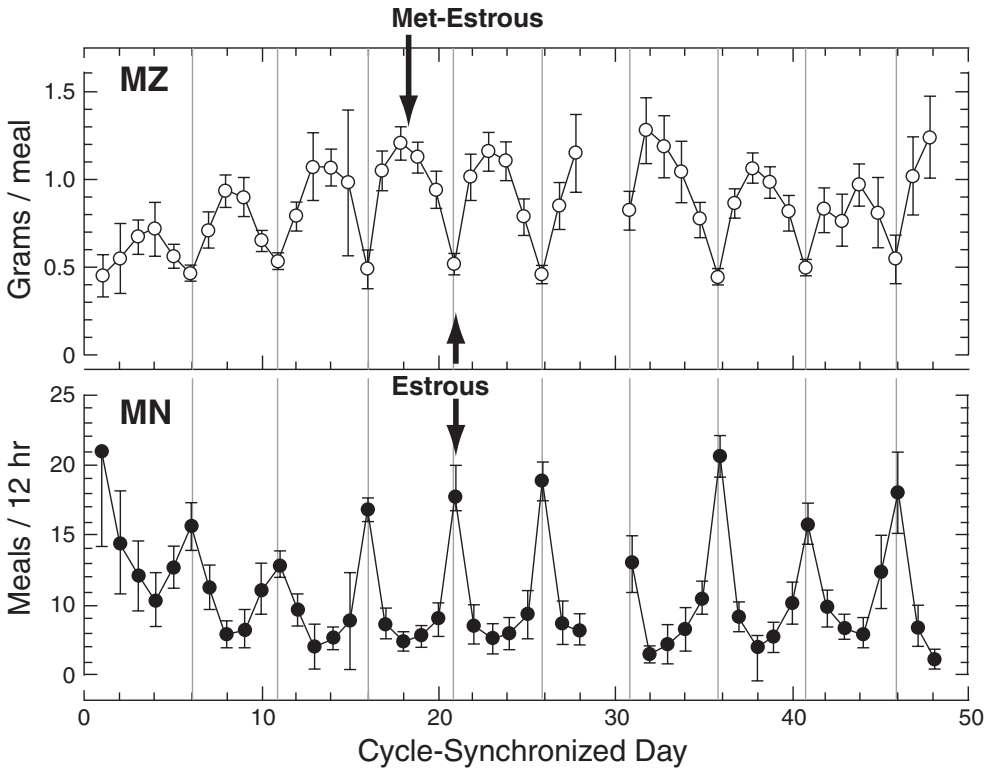

Fig. 6. Food intake in female rats is relatively stable by means of cyclical and reciprocally recurring changes in both meal size (MZ) and meal number (MN), which are synchronized with the 3–4 day estrous cycle), such that meal number is greatest during estrous phase and meal size is small, while during the met-estrous cycle meal size is largest and meal number is the lowest. (From Laviano et al., 1996).

circadian oscillator, to influence the daily rhythm of food intake by changes in both its own receptors and their activity, and by changes in diurnal rhythms of other critical neurotransmitters such as dopamine, norepinephrine, and serotonin, and receptors such as alpha 1, beta 1 and 2 in specific hypothalamic nuclei including the VMH and SCN which influence the response to the acute phase response via the HPA and cortisol response. Thus, Watanobe and Yoneda observed a greater release of ACTH in female than in male rats in response to the intravenous administration of lipoprotein polysaccharide (Watanobe and Yoneda, 2003). However there were no changes in plasma IL-1β, IL-6 or TNF-α. There were also no changes in tissue concentrations of CRF and arginine–vasopressin in the medial basal hypothalamus and in the anterior pituitary (AP). There were no changes in the binding characteristic of IL-6 in the medial basal hypothalamus or AP but the number of the IL-1β and TNF-α binding sites, but not in the binding affinities in the medial basal hypothalamus altered significantly after gonadectomy in response to a lipopolysaccharide challenge. These sexual differences were restored after hormonal restoration in response to lipopolysaccharide. The results suggest that the hypothalamic sensitivity to peripheral IL-1 β and TNF-α is an important mechanism underlying the sexual dimorphic ACTH response to lipopolysaccharide in rats.

In a recent study designed to gain insight into the sex differences of basic nonspecific and specific immune responses intracellular type I and II cytokine production by stimulated male and female lymphocytes and monocytes in a whole-blood preparation was measured by flow cytometry. An increased percentage of IL-12, IL-1β and TNF-α

was found in men compared to women suggesting that gender differences in the balance between specific and nonspecific immune response existed in men compared to women (Bouman et al., 2004; Posma et al., 2004). Thus, it is apparent that the acute phase response is different in males and in females, explaining in part, the greater survival of the female.

Overwhelming the acute phase response by massive accumulation of subcutaneous fat

The next example that we cite is based on our observations of obesity-induced inflammatory changes in adipose tissue (Hotamisligil et al., 1993; Wellen and Hotamisligil, 2003; Xu et al., 2003; Fantuzzi, 2005). In a series of studies Sprague–Dawley pups were made obese using a high-energy diet (Ramos et al., 2003). We found that the ratio of mesenteric fat to subcutaneous fat for IL-6, TNF-α, corticosterone and their gene profiles as measured by GeneChip Rat UG34A Gene Chip (Affymetrix, Santa Clara, CA) was significantly elevated relative to nonobese mesenteric fat and contributed to the hyperglycemic and hyperdyslipidemia of obesity. In response to weight loss induced by gastric bypass these inflammatory mediators normalized. As summarized schematically in Fig. 7, as obesity develops the size of the adipocyte increases, which stimulates it to increase the synthesis and release of TNF-α. This stimulates both pre-adipocyte and endothelial cells within the surrounding fat to produce monocyte chemo-attractant protein increasing further intraadipose migration of monocytes. The stimulated mature adipocyte also synthesizes leptin and vascular endothelial growth factor contributing to angiogenesis, while the accumulating free fatty acids induce oxidative stress to the vascular endothelium, in a similar process to arteriosclerosis. The infiltrating macrophages secrete IL-6, IL-1β, TNF-α and corticosterone. The net effect is to increase insulin resistance and induce the biochemical picture of type 2 diabetes mellitus.

Brain modulation of systemic inflammation: The nicotinic anti-inflammatory pathway

The last example that we would like to use is a recently completed experiment in our rat tumor model in which we have demonstrated cytokine production. This stimulus has been modified by the external application of nicotine.

As previously described, a large bulk of data exists showing that brain's activity including behavioral responses like feeding is heavily influenced by cytokines or in broader terms by inflammation. These interactions occurring at the cellular and molecular levels between inflammatory mediators and aminergic as well as peptidergic neurons explain the occurrence of fever, anorexia and cachexia, and may provide an important step based on which we can develop pathogenesis-based therapeutic strategies.

However, the hypothalamus not only integrates immune inputs to adjust metabolism and behavior, but it appears to influence the immune response as well. In other words, and probably via a feedback system already demonstrated in many physiologic responses, inflammation influences the brain which in turn influence inflammation. There is a good evidence that the brain, via the vagus nerve, can control systemic inflammation in animal models (Borovikova et al., 2000; Wang et al., 2003). In particular, it appears that acetylcholine, the main neurotransmitter of the vagus nerve, can inhibit the production of pro-inflammatory cytokines by signaling through nicotinic receptors of macrophages (Fig. 8; Ulloa, 2005). Consequently, this mechanism has been called "the nicotinic anti-inflammatory pathway," since acetylcholine exerts its anti-inflammatory effects via the a7-nicotinic–acetylcholine receptor (a7 nAChR; Wang et al., 2004). Interestingly, nicotine is more efficient than acetylcholine at inhibiting cytokine production since nicotine is a more selective cholinergic agonist. This evidence may explain the well-established clinical knowledge that Crohn's disease, which can be described as a chronic inflammatory status of the intestine mediated and sustained by cytokines, is less prevalent and severe among smokers than among nonsmokers.

The molecular mechanisms responsible for the anti-inflammatory effects of nicotine are currently being detailed. It appears that nicotine prevents the endotoxin-induced activation of the nuclear factor-κB (NF-κB) pathway, which is critical for the production of pro-inflammatory cytokines

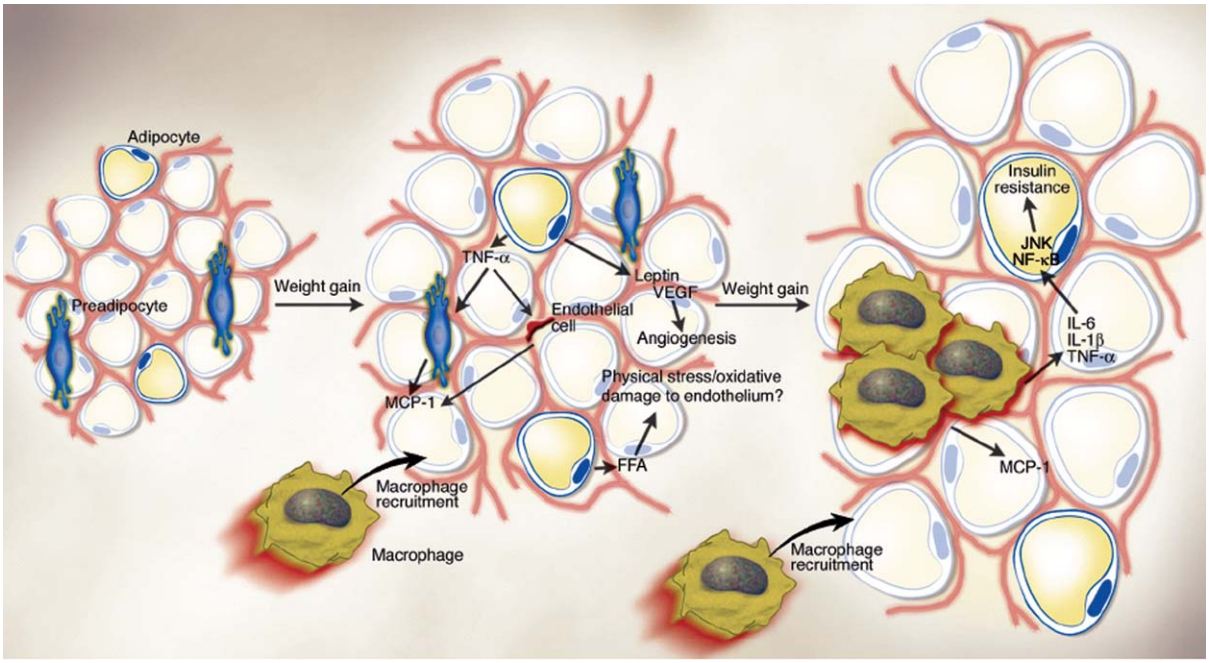

Fig. 7. Obese adipose tissue is characterized by inflammation and progressive infiltration by macrophages as obesity develops. Changes in adipocyte and fat pad size led to physical changes in the surrounding area and modifications of the paracrine function of the adipocyte. For example, in obesity, adipocytes begin to secrete low levels of TNF-α, which can stimulate preadipocytes to produce monocyte chemoattractant protein-1 (MCP-1). Similarly, endothelial cells also secrete MCP-1 in response to cytokines. Thus, either preadipocytes or endothelial cells could be responsible for attracting macrophages to adipose tissue. The early timing of MCP-1 expression prior to that of other macrophage markers during the development of obesity also supports the idea that it is produced initially by cells other than macrophages. Increased secretion of leptin (and/or decreased production of adiponectin) by adipocytes may also contribute to macrophage accumulation by stimulating transport of macrophages to adipose tissue and promoting adhesion of macrophages to endothelial cells, respectively. It is conceivable, also, that physical damage to the endothelium, caused either by sheer size changes and crowding or oxidative damage resulting from an increasingly lipolytic environment, could also play a role in macrophage recruitment, similar to that seen in atherosclerosis. Whatever the initial stimulus to recruit macrophages into adipose tissue is, once these cells are present and active, they, along with adipocytes and other cell types, could perpetuate a vicious cycle of macrophage recruitment, production of inflammatory cytokines, and impairment of adipocyte function. (From Wellen et al., 2003).

(Li and Verma, 2002), via a7 nAChR signaling (Wang et al., 2004).

The potential therapeutic exploitations of the nicotinic anti-inflammatory pathway are many, and are currently being tested. We have been previously shown that nicotine-induced reduction of food intake is mediated via derangement of brain neurochemistry (Miyata et al., 1999; Ramos et al., 2004a) in normal rats. More recently, we hypothesized that nicotine administration may improve food intake in anorectic tumor-bearing rats via its signaling through the nicotinic anti-inflammatory pathway. To test this hypothesis we used the Fischer rat-methylcholanthrene-sarcoma model, since this animal model of cancer-induced anorexia serves very well to the hypothesis since anorexia is mediated by systemic and central hyperproduction of TNF-α and IL-1 (Smith and Kluger, 1993; Opara et al., 1995a; Chance et al., 2003), and pharmacological inhibition of these two cytokines has been demonstrated effective in ameliorating anorexia (Torelli et al., 1999; Laviano et al., 2000). First, we tested whether repeated nicotine administration had any permanent effects on food intake of normal rats, and we observed that nicotine (three injections/day for three consecutive days each week) reduces food intake in a dose-dependent manner, as expected, but this effect progressively

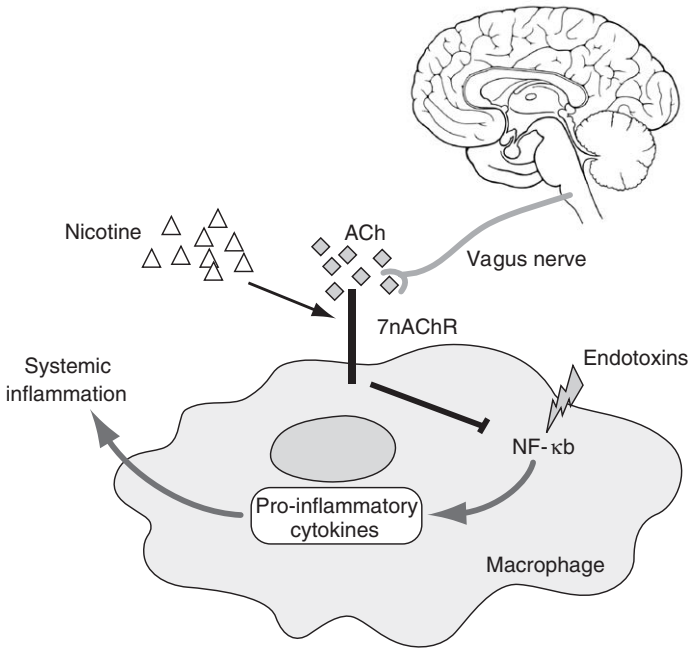

Fig. 8. After injury, injection or trauma, endotoxins activate a number of macrophage intracellular pathways, including the NF-κB pathway, which is critical for the production of proinflammatory cytokines. Cytokines then promote and sustain systemic inflammation. To compensate for the increasing inflammatory status, the vagus nerve releases acetylcholine (ACh) which signals through the a7-nicotinic-acetylcholine receptor (a7 nAChR) to inhibit NF-κB induced macrophage activation and cytokine production. Compared to ACh, nicotine is more selective at activating a7 nAChR and efficient at inhibiting proinflammatory cytokines. This pathway has been named as ''the nicotinic anti-inflammatory pathway'' (Adapted from Ulloa, 2005).

fades away with time, and disappears after 3 weeks. In tumor-bearing rats, we decided to test different injection schedules of the minimal effective dose, and preliminary results shows that repeated nicotine administration improves food intake in anorectic tumor-bearing rats and prolongs survival. Analyses are being carried out to test whether these important effects are associated with reduced production of pro-inflammatory cytokines.

Summary of afferent signals

The sums of these divergent and dissimilar studies reveal common immune responses that modify behavior and initiate an immune response by (i) monocytes elaborating cytokines in response to either a physiological or a pathological event; (ii) peripheral immune sensors detect these: the efferent vagal fibers in the gut/liver or the somatic preganglionic fibers in the tissue; and (iii) transduced via an increase in vagal efferent activity is transmitted to the dorsomotor vagal complex of the medulla, which projects onto the hypothalamus including the preoptic area with activation of the PVN (Elmquist and Saper, 1996); (iv) an afferent neural response leads to an increased release of T cells from the thymus and a delayed uptake and destruction of B cells by the spleen and (v) a neuroendocrine event occurs between the hypothalamic nuclei to modulate the metabolic event via the HPA axis.

Central Integration

Figure 9 shows the relationship between the first- and second-order neurons in the ARC, and their susceptibility to hormones and cytokines. Much data contributing to our understanding of central regulatory function has emanated from our studies on continuous intravenous infusion of nutrients and cancer anorexia.

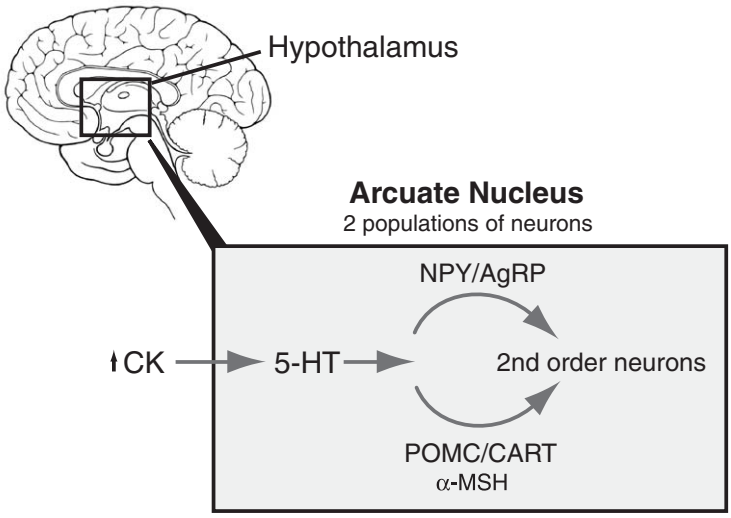

Fig. 9. Peripheral signals such as cytokines (CK) reach the hypothalamus, specifically the arcuate nucleus (ARC), where they interact with two neuronal populations, which project to second-order neuronal signalling pathways. Neuropeptide Y/Agouti-related peptide (AgRP) neurons stimulate food intake. Pro-opiomelanocortin (POMC)/cocaine and amphetamine-regulated transcript (CART) neurons inhibit food intake. The effects of cytokines on hypothalamus seem to be mainly mediated by 5-HT. (From Laviano, et al., 2003).

As tumor progresses and grows, interaction between tumor and immune system are established affecting body metabolism from cellular to behavioral level both peripherally and centrally. Tumor growth leads to anorexia (food intake reduction) (Meguid et al., 1987; Kurzer et al., 1988; Makarenko et al., 2003; Meguid et al., 2004; Ramos et al., 2004c). Cytokines acting in endocrine, paracrine and autocrine fashion, play a key role in this relationship establishing a link between tumor and metabolism as well as behavior. During tumor development there is an imbalance between pro-inflammatory, IL-1, IL-6, TNF-α and anti-inflammatory cytokines, such as IL-10, that causes changes in monoaminergic and peptidergic systems, most of them identified in feeding and energy homeostasis control, in both whole brain and hypothalamus (Noguchi et al., 1996; Cravo, 2000; Plata-Salaman, 2000; Makarenko et al., 2002, 2003).

Although there is much evidence showing the involvement of peripheral IL-1 in cancer anorexia pathogenesis, it has been demonstrated that IL-1 is also synthesizing at CNS which together with that synthesized peripherally acts directly in the CNS to inducing anorexia (Gelin et al., 1991; Plata-Salaman, 1991; Plata-Salaman and Ffrench-Mullen, 1992; Yang et al., 1994; Plata-Salaman et al., 1998; Turrin et al., 2004). Cytokine receptors have been found in the CNS including hypothalamus (Cunningham and De Souza, 1993) with highest abundance in VMH (Yabuuchi et al., 1994). Furthermore, small pathophysiological dose of IL-1α are required to induce anorexia when these are injected centrally, while pharmacological dose are needed to obtain the same effect when injected peripherally (Plata-Salaman, 1996; Plata-Salaman et al., 1996). We measured the content of IL-1α in cerebrospinal fluid obtained from tumor-bearing rats, achieved by inoculation of methylcholanthrene-induced sarcoma cells, finding reduction of food intake in tumor-bearing rats during anorectic phase compared to pre-anorectic phase as well as to controls. Furthermore, cerebrospinal fluid IL-1α correlated negatively with food intake and positively with tumor weight (Opara et al., 1995a) indicating that central IL-1α plays a role in the pathogenesis of cancer anorexia to conserve energy and to induce mobilization of nutrients for the defense of the host. The data also suggest that other anorectic cytokines (IL-6, IL-8 and TNF-α) may contribute to this phenomenon. These data agree with previous reports showing

that IL-1α, IL-1β, IL-8 and TNF-α exert a general anorectic effect at the central level (Chance and Fischer, 1991; Plata-Salaman and Ffrench-Mullen, 1992; Fantino and Wieteska, 1993; Plata-Salaman and Borkoski, 1993; Yang et al., 1999).

Arcuate nucleus

Several experimental findings point the ARC as one of the hypothalamic structures playing a role in the effects of cytokines, particularly IL-1. The medial part of the ARC contains cells that express IL-1R1 (Ericsson et al., 1995) and is activated by systemic IL-1 administration (Herkenham et al., 1998; Reyes and Sawchenko, 2002). Besides, the medial part of the ARC can bind peripheral peptides or proteins because of its localization close to median eminence.

MohanKumar et al. (1999) showed in adult male rats that after intraperitoneal administration of lipopolysaccharide (10 μg/kg body weight) there was an increase (more than twofold) in DA concentrations on ARC compared to control rats. However, lipopolysaccharide treatment did not alter the content of other neurotransmitters, such as 5-HT, NE or its metabolites, in ARC. IL-1β may mediate these changes in DA given that the pretreatment with IL-1ra avoid the increase in DA content (MohanKumar et al., 1999; Fig. 10). In addition, systemic lipopolysaccharide administration increases noradrenergic and serotonergic metabolism (Delrue et al., 1994) and activates tryptophan hydroxylase (the first enzyme in the route of synthesis of monoamines) and tyrosine hydroxylase (the rate-limiting enzyme in monoamine synthesis) in several brain areas including ARC, PVN and posterior pituitary gland (MohanKumar et al., 1999; Nolan et al., 2000; De Laurentiis et al., 2002). In a more recent study, Gonzalez et al. (2004) found that intracerebroventricular injection of lipopolysaccharide in male rats caused a transitory and strong immunoreaction to IL-1β in ARC microglial cells parallel with a decline in the number of tyrosine hydroxylase-and tyrosine hydroxylase mRNA-positive cells and in tyrosine hydroxylase activity (the rate-limiting enzyme in monoamine synthesis) in median eminence and, at 12 h, an elevation in prolactin concentrations in serum. These results suggest that hypothalamic catecholaminergic system are involved in the control of autonomic and neuroendocrine responses to peripheral and central inflammation.

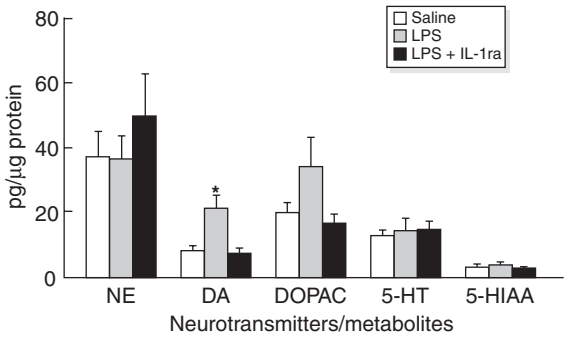

Fig. 10. Effects of lipopolysaccharide (LPS) on neurotransmitter concentrations in the arcuate nucleus (ARC). Lipopolysaccharide treatment increased the concentration of DA in the ARC $p < 0.05$. Treatment with IL-1ra completely blocked this effect. Other neurotransmitters were unaffected. (From MohanKumar et al., 1999).

Other hypothalamic systems involved in the regulation of energy homeostasis affected by cytokines are neuropeptide Y (NPY) and α-MSH and pro-opiomelanocortin (POMC). Thus, in tumor-bearing rats at the onset of anorexia NPY immunoreactivity in ARC was lower than in non-tumor-bearing rats while α-MSH was greater (Ramos et al., 2005) and these changes were reverted when the rats were fed with ω-3FA as well as the inhibition of food intake. In tumor-bearing rats fed with ω-3FA diet NPY immunoreactivity in ARC was greater than in tumor-bearing chow-fed rats (Ramos et al., 2005). After peripheral administration of IL-1β in rats Reyes and Sawchenko, (2002) detected greater percentage of activated neurons expressing NPY, which co-express Agouti-related peptide (AgRP) (Broberger et al., 1998) and POMC, which co-express Cocaine-amphetamine regulated transcript (CART) (Elias et al., 1998), than after vehicle administration by measuring of Fos induction and these changes were accompanied by a decline in food intake.

In a recent study carried out in C57BL/6J mice, Rossi-George et al. (2005) have described a

significant increase in cFos expression in ARC, as well as in PVN, after intraperitoneal injection of 10 μg of staphylococcal enterotoxin A, a superantigen that activates T lymphocytes and induces production of different cytokines such as TNF-α, INT-γ and IL-2 (Bette et al., 1993; Rosendahl et al., 1997) and have neurobiological actions including the activation of HPA axis, sympathetic nervous system and anorexia (Shurin et al., 1997; Kusnecov et al., 1999; Del Rey et al., 2002; Pacheco-Lopez et al., 2004), or 5 μg of lipopolysaccharide (Fig. 11A) along with a reduction in food intake associated to anxiety/fear-like process and to cFos activation in limbic brain regions. The cFos induction after staphylococcal enterotoxin A seems to be mediated by TNF-α, which

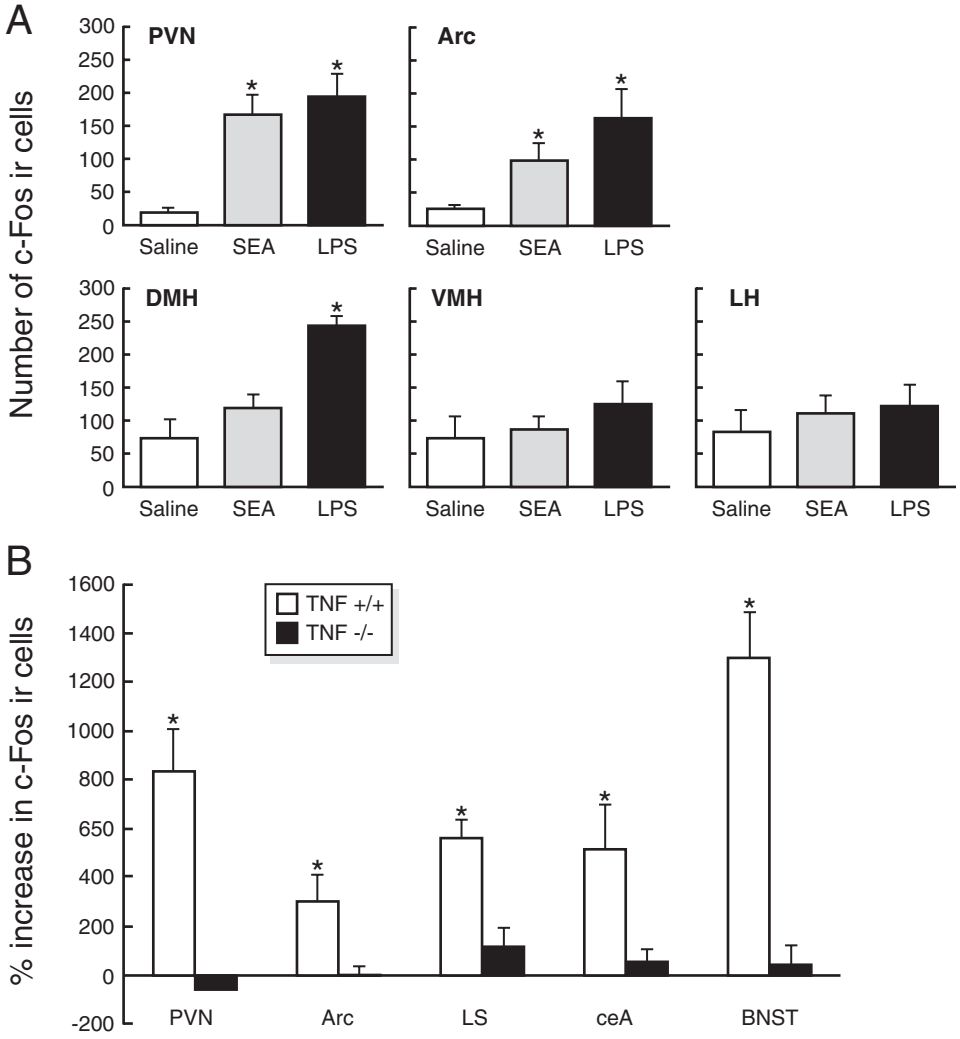

Fig. 11. (A) Mean number of c-Fos-immunoreactive cells in hypothalamic nuclei 2 h after intraperitoneal injection with saline, 10 μg of SEA, or 5 μg of lipopolysaccharide (LPS). Each bar represents the mean ± SEM. *$p < 0.05$ relative to saline. (B) Percentage increase in the number of c-Fos-immunoreactive cells in the brains of SEA-challenged wild-type (TNF + / +) and TNF-α knockout (TNF-/-) mice. For each individual animal that was given an injection of SEA, the quantitation for each brain region was expressed as a percentage above the group mean of the corresponding saline-injected control of the same strain. The mean number of c-Fos-positive cells in wild-type saline-injected and saline-injected TNF-α knockout mice did not differ. (From Rossi-George et al., 2005).

plasma levels were increased after staphylococcal enterotoxin A injection, given that in TNF−/− mutant mice cFos induction was not observed (Rossi-George et al., 2005; Fig. 11B).

Paraventricular nucleus

Elmquist and Saper (1996) demonstrated, using cFos as an immunohistochemical marker of neuronal activity, that neurons in both the autonomic and endocrine components of the PVN were activated by lipopolysaccharide. Several of the activated cell groups directly projected to the PVN including the visceral motor complex, median preoptic nucleus, ventromedial preoptic area, nucleus of the stria terminalis, parabrachial nucleus, ventrolateral medulla and nucleus tractus solitarius. These findings indicate that the stimulation of the immune system activates cell groups from medial nervous systems that project on to the PVN and are consistent with the postulate that the PVN plays a key role in integrating diverse physiological cues into the varied manifestations that constitute the cerebral component of the acute phase response (Elmquist and Saper, 1996).

Cytokines induce their anorectic effects partly via the effects on the neurons of the PVN. In support of this, anorexia induced by experimental colitis in rats can be prevented by intracerebroventricular administration of IL-1ra that leads to a 18-fold reduction in PVN 5-HT associated with a significant increase in food intake (El-Haj et al., 2002).

In normal rats, the inhibition of 5-HT synthesis or the blockage of their receptors in PVN causes an increase of NPY concentration suggesting a link between both regulators (Currie and Coscina, 1997). This corresponds to the data that reports an inhibition in NPY system in different types of anorexia (Pich et al., 1992; Broberger et al., 1997, 1999), particularly those achieved after ventricular administration of ciliary neurotrophic factor, known to cause a decrease in NPY gene expression (Pu et al., 2000), or those associated with cancer (Chance et al., 1994a, b, 1998). Under these experimental conditions the injection of NPY into the PVN in tumor-bearing rats results in a decrease in food intake while in their pair-fed controls a significant increase in food intake occurs, suggesting a refractory feeding response to NPY in the tumor-bearing rats mediated by unknown mechanisms (Chance et al., 1994a; Inui, 1999). Furthermore, the infusion of NPY into the III ventricle inhibits and reverses the anorexia induced by both pathophysiological and pharmacological concentrations of IL1-β (Sonti et al., 1996). As shown in Fig. 12, our results are in keeping with these data, revealing a significant reduction in the NPY in PVN of tumor-bearing rats (Ramos et al., 2004c) accompanied by an increase in PVN 5-HT. Figure 13 of immunohistochemical sections of the hypothalamus, support the finding by showing increased staining of 5-HT_{1B} receptor proteins, indicating, that there is substantial serotoninergic innervations in PVN (Card and Moore, 1988; Makarenko et al., 2005b). NPY, one of the most potent orexigenic agents (Dryden et al., 1994) can affect many different neuronal systems given its wide distribution and its ubiquitous receptors in the hypothalamus. Of these the serotoninergic system has co-receptors (Fig. 13) since, as we have mentioned above, there is a close association between NPY-ir fibers and hypothalamic neurons expressing 5-HT_{1B} receptor in normal and in tumor-bearing rats (Makarenko et al., 2002). This interaction is bi-directional, since, in normal rats, an increase in NPY release with its subsequent enhanced of intake in food, has been reported after PVN injection of 5-HT receptor antagonist (Dryden et al., 1995). Furthermore, intraperitoneal or intracerebroventricular injection of serotonin agonist decrease the NPY concentration and inhibit stimulatory effect on food intake (Rogers et al., 1997; Currie et al., 2002). In recent studies, we have reported in tumor-bearing rats abnormal levels of hypothalamic 5-HT, NPY and DA at the onset of anorexia (Fig. 14). There is an increase in PVN 5-HT concentrations along with a decrease in NPY and DA concentrations. To confirm these findings, the tumor was resected with the expectation that the observed changes normalized. After tumor resection, food intake subsequently normalized and the concentration of both the monoamines and the NPY also return to normal values (Meguid et al., 2004; Ramos et al., 2004c). Using a pair fed vs. control group we verified that the reduction of food intake was induced by the changes observed in NPY and 5-HT in the tumor-bearing

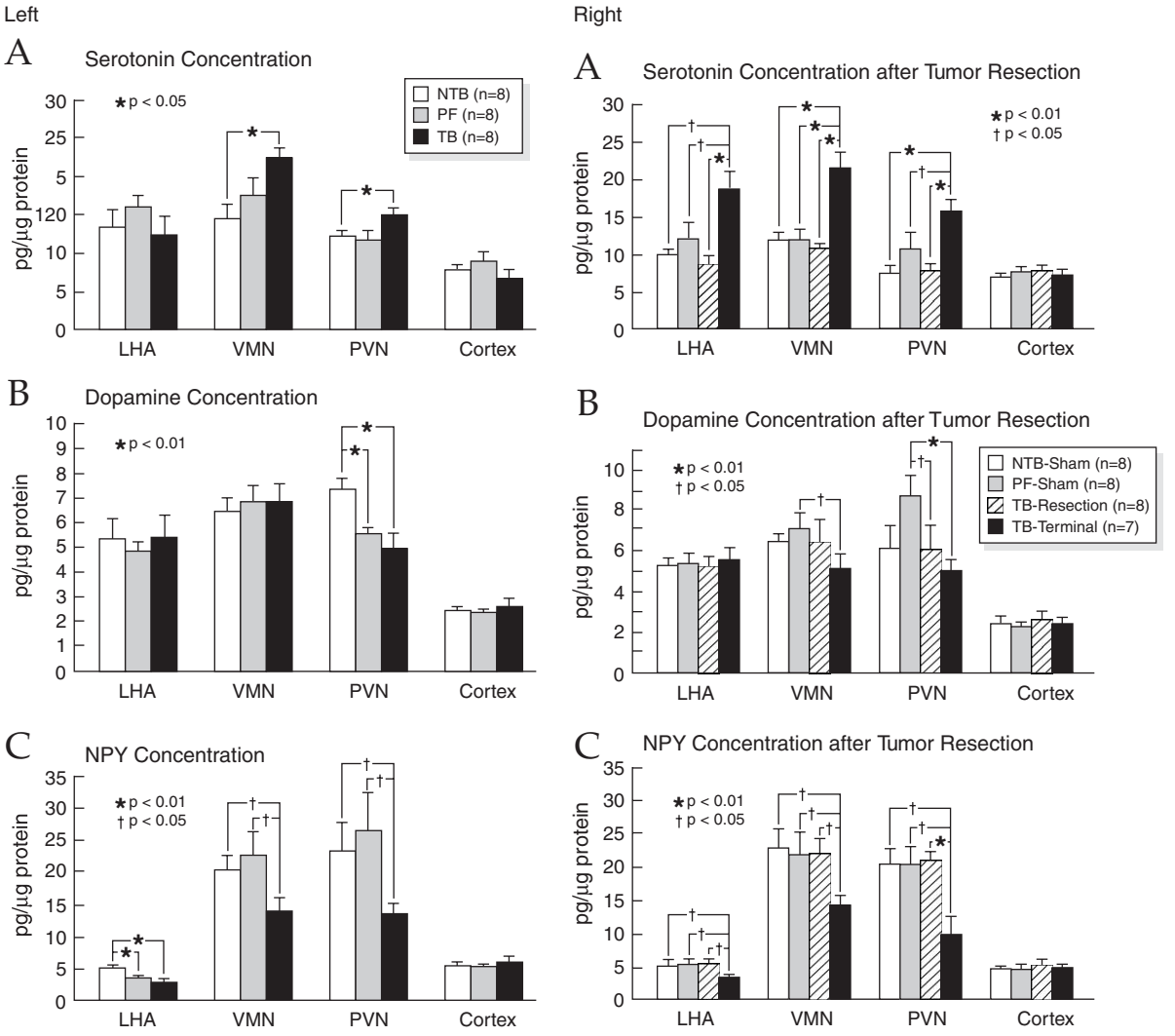

Fig. 12. Hypothalamic serotonin, and DA and NPY concentrations in LHA, VMN, and PVN at the onset of anorexia (left) and after tumor resection and terminal state (right). In tumor-bearing rats there was a significant reduction in the NPY in PVN of tumor-bearing rats accompanied by an increase in PVN 5-HT and an increase in bilateral VMH 5-HT content with a concomitant decrease of DA concentrations content while NPY decreases. LHA 5-HT content was increased in rats who were allowed to live until terminal state, while LHA NPY concentration was lower in tumor-bearing rats than in non-tumor-bearing rats at both the onset of anorexia (mean day 19) and at terminal state. (From Ramos et al., 2004c).

rats, while DA reduction seems to be due to the decrease in food intake because the decline in food intake also occurred in the pair-fed group. These data suggest the existence of a dynamic interaction between brain amines and NPY in tumor-bearing rats.

The changes in serotoninergic system at the onset of anorexia not only affect the levels of this neurotransmitter, but also the expression of 5-HT_{1B} receptors, one of the most important serotonin receptors mediating the anorectic effect of 5-HT receptors (Barnes and Sharp, 1999; Makarenko et al., 2002), as we have reported very recently (Makarenco et al., 2005a) using a peroxidase–antiperoxidase immunocytochemical methods and semiquantitative image analysis of 5-HT_{1B} receptors immunostaining. This study

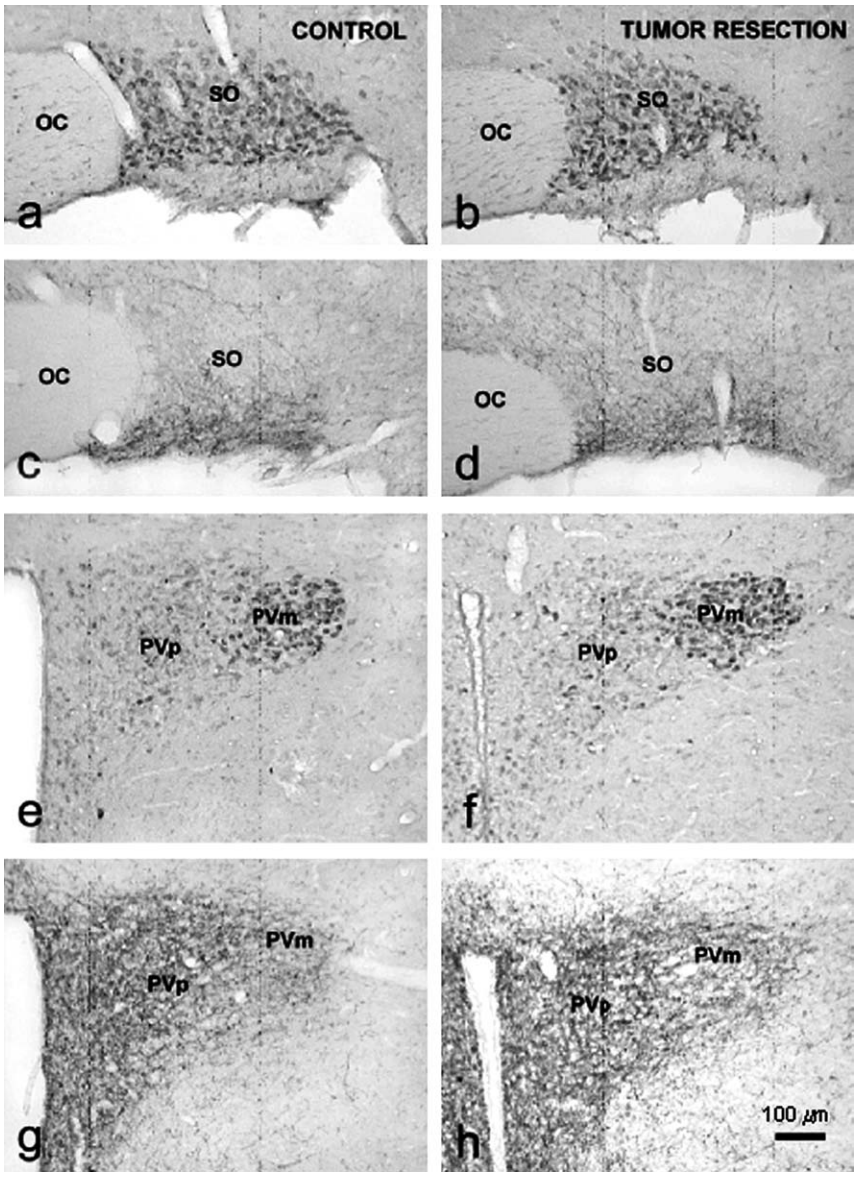

Fig. 13. Immunocytochemical visualization of 5-HT_{1B}-receptors (a, b, e and f) and NPY immunoreactive fibers (c, d, g and h) in the hypothalamus of Control and tumor resected (TB-R) rats. SO, supraoptic; PVm, magnocellular part of paraventricular nucleus; PVp, parvocellular part of paraventricular nucleus; OC, optic chiasm. In tumor-bearing rats there was an increased staining of 5-HT_{1B} receptor proteins indicating a substantial serotoninergic innervations in PVN. (From Makarenko et al., 2005b).

shows the same hypothalamic distribution of this receptor in both tumor-bearing rats and non-tumor-bearing rats, but higher immunostaining intensity in most neurons of the magnocellular PVN (but not in parvocellular division). It is generally accepted that most of the magnocellular neurons of the PVN, and also of the SON, produce oxytocin and vasopressin (Sawchenko and Swanson, 1983), which besides their involvement in water balance control, participate in feeding regulation exerting an anorectic action (Arletti et al., 1990; Olson et al., 1991). The activation of

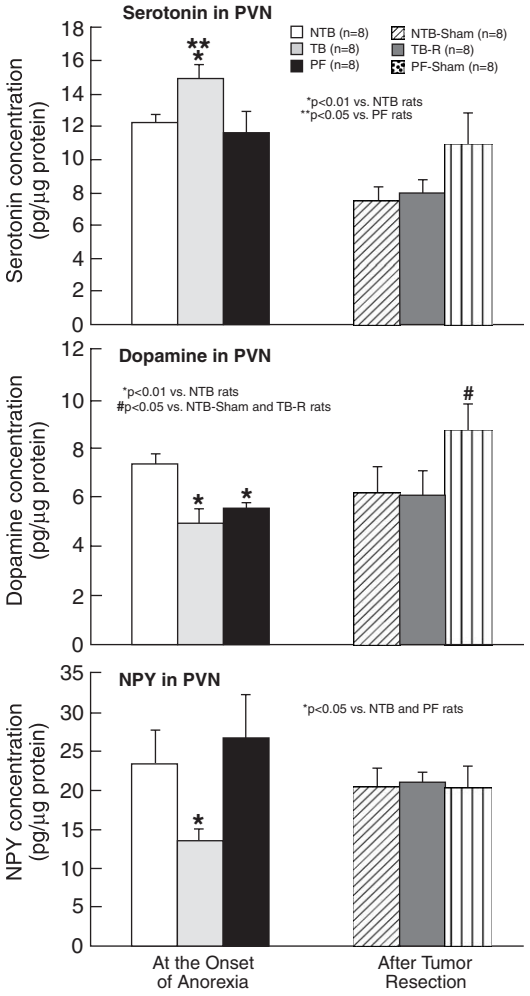

Fig. 14. Hypothalamic PVN 5-HT, DA and NPY concentrations. In tumor-bearing rats, there was an increase in PVN 5-HT concentrations along with a decrease in NPY and DA concentrations. These changes normalized after tumor resection. Values are mean ± SEM. *$p < 0.01$ vs. NTB rats; **$p < 0.05$ vs. PF (pair fed) rats. *# $p < 0.05$ vs. NTB (Sham) and tumor-bearing rats. (From Meguid et al., 2004).

5-HT_{1B} receptors on the magnocellular neurons modulates the release of both hormones and in turn food intake. Furthermore, it has been described that more than 95% of the oxytocin and vasopressin neurons in SON and PVN also express NPY-Y_5 receptors (Campbell et al., 2001). In a subsequent study using the same methods as we used in our reported studies we showed that the changes reported at the onset of anorexia in hypothalamic distribution of NPY and 5-HT_{1B} receptors are reverted after tumor resection (Makarenko et al., 2005a). These data show that tumor resection, and therefore the removal of the effect of cytokines, results not only in an enhancement of food intake, reaching the normal levels, but also in a reversible changes of hypothalamic orexigenic and anorectic modulators.

Ventromedial hypothalamus

As indicated by the data of Elmquist and Saper (1996) another primary hypothalamic site where cytokines regulates metabolism is VMH, a known satiety center, which send potent excitatory signals to ARC POMC neurons (Sternson et al., 2005). We injected a pathophysiological quantity of IL-1α into the VMH of rats and caused a significant reduction of food intake (Yang et al., 1999). The mechanism of action may involve the modulation of the serotoninergic and dopaminergic systems, because when we were measuring the release of 5-HT and DA's metabolites we found an increase in the concentrations of 5-HT, 5-HIAA (the main metabolite of 5-HT) and DA just after the injection of IL-1α in VMH. This remained above basal levels during the next 40–60 min, respectively (Yang et al., 1999), clearly linking the anorectic effect of IL-1α and the early development of satiety to neurotransmitters, particularly enhance serotoninergic activity. Other authors have also demonstrated the relationship between cytokines and hypothalamic neurotransmitters (Plata-Salaman, 1997). These interactions also extend to neuropeptides and hormones, because Smagin et al. (1996) reported an enhancement in NE hypothalamic content concurrent to an increase in plasma ACTH and corticosterone concentrations after both intravenous and intraperitoneal injection of IL-1β, indicating that the anorectic effect of this cytokine can be mediated by an increase in hypothalamic NE given that this neurotransmitter regulate HPA axis (Plotsky et al., 1989).

In tumor-bearing rats, we have found an upregulation of D_1- and D_2- receptor mRNA expression in VMH during anorectic period (Sato et al., 2001b, Fig. 15). Our data suggest that tumor-released

cytokines regulates food intake through modulation of dopaminergic activity that may take place in VMH as well as in SON (Sato et al., 2001b, a). It has been demonstrated that VMH serotoninergic activity enhanced during cancer anorexia in methylcholanthrene tumor-bearing rats and returned to control levels along with a normalization of food intake once tumor was removed supporting the involvement of serotoninergic system in IL-1α-induced anorexia (Blaha et al., 1996). Furthermore, VMH microinjection of mianserin, 5-$HT_{1c/2}$ antagonist receptor, or IL-1ra, an endogenous inhibitor of IL-1α in anorectic methylcholanthrene tumor-bearing rats improve food intake by an increase in meal number without effect on meal size, as measured using the Automated Computerized Rat Eater Meter (Meguid et al., 1990), while in normal rats this effect does not occur (Laviano et al., 2000). These findings suggest that under normal conditions VMH 5-HT has only a relative importance in the control of meal number and meal size. However, during tumor growth VMH 5-HT participation in the control of food intake homeostasis becomes relatively important. By integrating these data we suggest that during the progressive tumor growth IL-1α may cause anorexia by a central mechanism that involves VMH 5-HT (Kuriyama et al., 1990).

As shown in Fig. 12 Ramos et al. (2004c) found an increase in bilateral VMH 5-HT content with a concomitant decrease of DA concentrations content in tumor-bearing rats at the onset of anorexia, while NPY decreases. These changes, that were accompanied by a reduction in total body fat in tumor-bearing rats as well as a significant decrease of food intake, are normalized 9 days after tumor resection, while these indices continued to be abnormal in tumor-bearing control rats until death.

Lateral hypothalamic area

In our studies, as shown in Fig. 12, 5-HT and DA concentration in LHA in tumor-bearing rats was not significantly different from nontumor-bearing rats at the onset of anorexia but 5-HT content was increased in rats which were allowed to live until the terminal state, while NPY concentration was lower in tumor-bearing rats than in nontumor-bearing rats at both onset of anorexia (mean day 19) and at the terminal state. And these changes were accompanied by a significant reduction in food intake during the study and thus were associated with a reduction in total body fat (Ramos et al., 2004c). As described above, after tumor resection, performed to validate the tumor as the etiology of the acute phase response cytokine changes, the changes reported had reverted 9 days after tumor resection, while these indices continued to be abnormal in their tumor-bearing control cohorts until their death.

In tumor-bearing rats there is an increase of mRNA of both D_1- and D_2- receptor in LHA (Sato et al., 2001b; Fig. 15). Furthermore, LHA

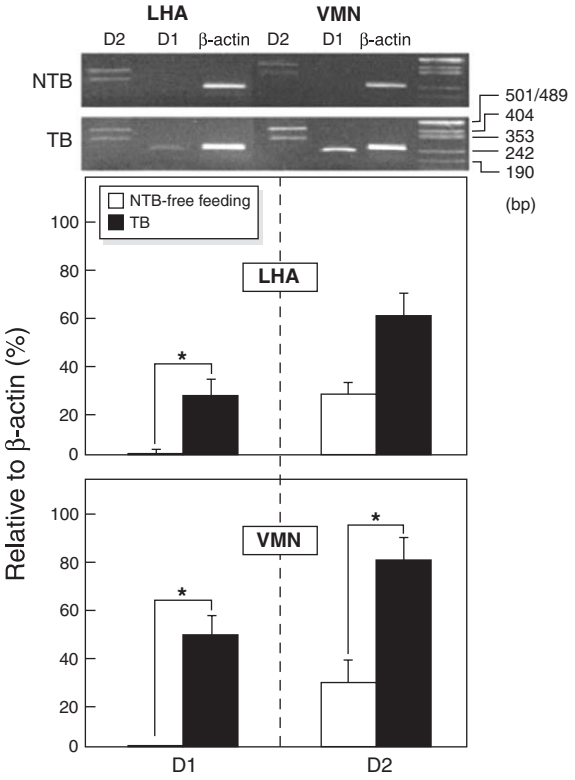

Fig. 15. D_1- and D_2-receptor mRNA expression in the LHA and VMN in anorectic tumor-bearing and non-tumor-bearing free-feeding control rats. Data are expressed as percent change relative to β-actin (β-Act). $*p<0.05$. In tumor-bearing rats, an upregulation of D_1- and D_2- receptor mRNA expression in VMH and LHA during anorectic period was found. (From Sato et al., 2001b).

DA release is increased during cancer anorexia (Chance et al., 1991). However, using microdialysis, we found that continuous peripheral IL-1α infusion in normal rats did not cause modifications in LHA DA content (Yang and Meguid, 1995), suggesting that other cytokines were also a contributory factor involved in the biochemical changes observed in LHA in cancer anorexia.

Supraoptic nucleus

The SON, besides its participation in the control of water balance, are also involved in the regulation of food intake by mean of the secretion of vasopressin and oxytocin (anorectic neurohypophyseal hormones) into hypothalamic–pituitary portal circulation (Arletti et al., 1989: Langhans et al., 1991b) after stimulation of D_2 receptors by DA released by dopaminergic neurons from the ventrotegmental area in the brain stem. Sato et al. (2001a) have reported that an injection of D_2 receptor antagonist (sulpiride, 4 μg/0.5 μl) into bilateral SON of anorectic tumor-bearing rats results in an increase in both meal size and meal number leading to an improvement of food intake (Fig. 16) and therefore in body weight as we have also observed when sulpiride was injected into LHA and VMH (Sato et al., 2001b), although in these nuclei the increase in food intake is achieved by an increase in meal number only.

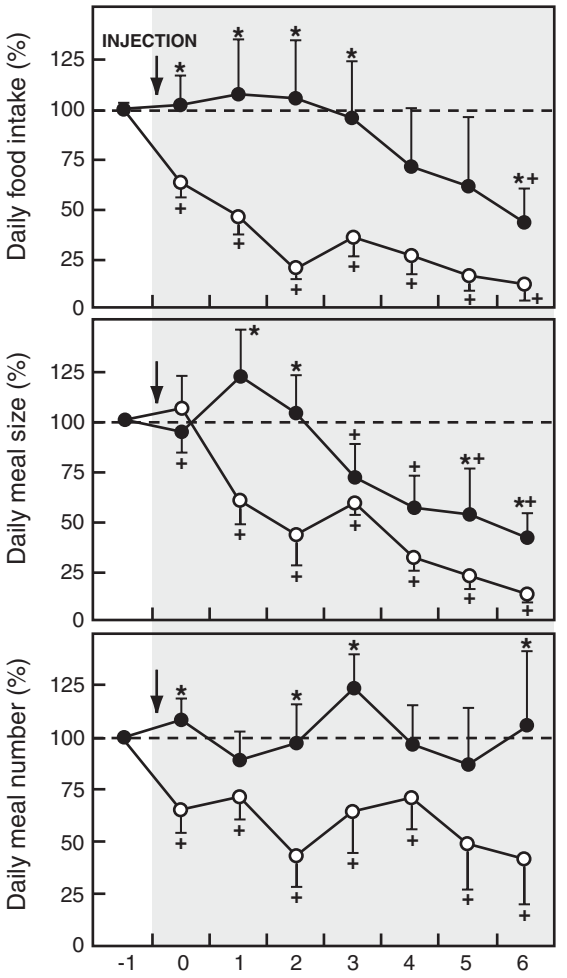

Fig. 16. Changes in food intake (top panel), meal size (middle panel) and meal number (lower panel) after an injection of sulpiride/saline into the supraoptic nucleus in tumor-bearing rats. Food intake, meal size and meal number on day −1 before injections was defined as 100%. $*p<0.05$ vs. control group. $+p<0.05$ vs. data on day 0 in each group. D_2 receptor antagonist injection caused an increase in both meal size and meal number leading to an improvement of food intake. (From Sato et al., 2001a).

Efferent response of acute phase response

During infection, tissue injury, inflammatory or malignant process immune-derived cytokines exert strong neuroendocrine effects resulting in marked changes in host homeostasis. One of the most affected metabolic pathways is carbohydrate metabolism. IL-1, one of the main inflammation mediators, has the capacity to elevate glucocorticoid levels by stimulating hypothalamic CRF-producing neurons (Berkenbosch et al., 1987; Sapolsky et al., 1987; Del Rey et al., 1998). It has been observed that IL-1β intraperitoneal administration increases glucocorticoid and glucagon production, that stimulate the mobilization of glucose stores, and decreases hepatic glycogen content in mice, but these changes are accompanied by hypoglycemia (Del Rey and Besedovsky, 1987; Del Rey et al., 1998) which is even more marked under fasting conditions and is sustained even after glucose load (Fig. 17), suggesting that the glucose fast mobilized from the liver is rapidly incorporated into other tissues such as fat or muscle by an increase in glucose transport elicited by IL-1

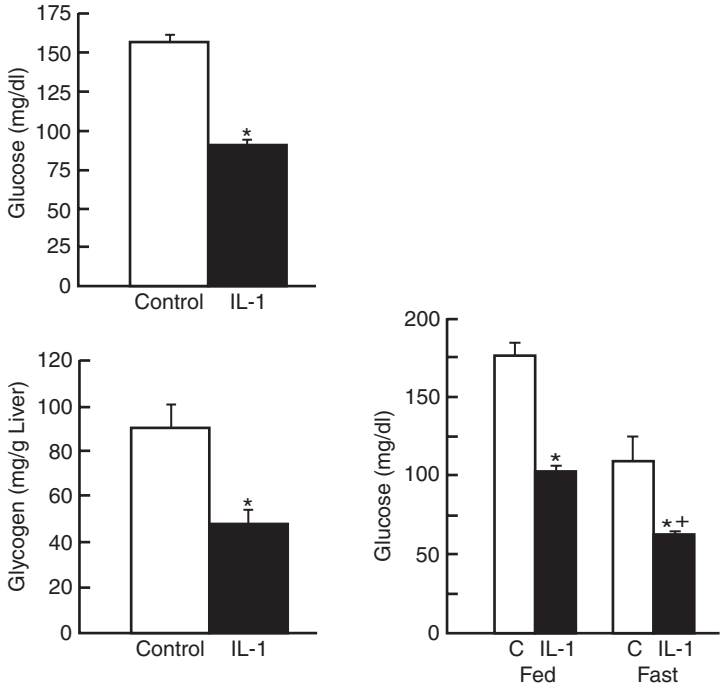

Fig. 17. Intraperitoneal injection of IL-1β induced hypoglycemia accompanied by a decrease in glycogen content in mouse liver (left). Each bar represent mean ± SEM. *$p < 0.05$ vs. control mice, + $p < 0.05$ vs. *fed* ad libitum mice. The hypoglycemia is even more marked under fasting conditions (24 h fasting, right). (From Del Rey et al., 1998).

(Garcia-Welsh et al., 1990; Bird et al., 1990; Shikhman et al., 2001; Fischereder et al., 2003). Further, it has been demonstrated that 2-deoxy-glucose uptake by peripheral tissues (heart, spleen, lung, liver and tumor) was enhanced in mice bearing IL-1β-secreting tumor (Metzger et al., 2004); this increase in glucose uptake may be mediated by a nondependent insulin enhancement of hepatic mRNA expression of the glucose transporter 3 (GLUT-3) by IL-1β. IL-1β, as well as IL-6, inhibit the enhancement of glycogen deposition induced by insulin in primary rat hepatocyte cultures increasing [^{14}C]-glycogen degradation, decreasing [^{14}C]-glucose incorporation into glycogen, stimulating glycogen phosphorylase activity and inhibiting glycogen synthase activity (Kanemaki et al., 1998) which are the rate-limiting enzymes in glycogen metabolism. It was also reported that the inhibition of glycogen synthesis by pro-inflammatory cytokines in both in vitro and in vivo models by Kitano et al. (2002) and Metzger et al. (2004) respectively, as well as the inhibition of gluconeogenesis in vitro by Yerkovich et al. (2004). It has been observed that cytokines inhibit gluconeogenesis induced by glucagon (Stadler et al., 1995; Christ and Nath, 1996). The inhibition of hepatic glucose synthesis was elicited by a down-regulation of phosphoenolpyruvate carboxykinase and glucose-6-phosphatase activities induced by cytokines (Metzger et al., 2004; Yerkovich et al., 2004) as well as by the action of cytokines on other enzymes of gluconeogenesis or glycolysis (Ceppi et al., 1992; Metzger et al., 1997; Maitra et al., 2000).

The hypoglycemic effect of cytokines may be due to, at least in part, an increase in insulin levels (Del Rey and Besedovsky, 1987) but is more probable that it can be mediated by activation of brain IL-1 receptors (Del Rey et al., 1998) given that the hypoglycemic effect was also found in insulin-resistant diabetic mice and in adrenalectomized mice, where there is no hyperinsulinemia (Del Rey and Besedovsky, 1989), and this central action may involve effects on central mechanisms

controlling glucose homeostasis leading to a downregulation of glucose set point (Del Rey and Besedovsky, 1992; Del Rey et al., 1998). In this central effect of IL-1, hypothalamic catecholamines seen to play a role counteracting the effect of cytokines on glucose concentrations given that its central depletion accentuated hypoglycemia. (Del Rey et al., 1998).

One of the interfaces between cytokines and glucose metabolism may be 5-HT, as was proposed by MohanKumar et al. (1999). These authors suggest that the increase in PVN 5-HT activity observed in rats after lipopolysaccharide intraperitoneal injection, which is mediated by IL-1β, could play a role in HPA axis activation given that 5-HT fibers innervate CRF perikarya (Sawchenko et al., 1983) and changes in PVN 5-HT concentrations markedly altered CRF release (Feldman et al., 1987).

During inflammation and infection process there are many changes in host lipid and lipoprotein metabolism including an increase on adipose tissue lipolysis, hepatic reesterification of fatty acid and hepatic lipogenesis as well as a decline in fatty acid oxidation in several tissues such as liver, heart and skeletal muscle (Lanza-Jacoby and Tabares, 1990; Takeyama et al., 1990; Feingold et al., 1992; Hardardottir et al., 1994; Khovidhunkit et al., 2004). These changes can be achieved by administration of lipopolysaccharide and pro-inflammatory cytokines suggesting that these proteins are involved in the mediation of many of the host metabolic responses that take place during inflammation and infectious diseases (Hardardottir et al., 1994). Many of these effects of cytokines on lipid metabolism are mediated by the modulation of synthesis and activity of some enzymes involved in the metabolism of lipids. For example, lipopolysaccharide and cytokines reduce mRNA expression of fatty acid translocase and fatty acid transport protein in muscle, heart and adipose tissue of Syrian hamster (Memon et al., 1998a). Further, lipopolysaccharide, TNF-α and IL-1 decrease mRNA levels and activity of acyl-CoA synthetase in several tissues including liver and adipose tissue of Syrian hamster (Memon et al., 1998b; Fig. 18) enhancing fatty acid reesterification, suppressing fatty acid oxidation and stimulating lipogenesis and therefore leading to elevated plasma triglycerides and very low-density lipoprotein (Feingold et al., 1991; Memon et al., 1993; Nachiappan et al., 1994).

Besides these effects on carbohydrate metabolism, IL-1 acts on protein and lipid metabolism (Del Rey and Besedovsky, 1987; Klasing, 1988; Argiles et al, 1989; Kanemaki et al., 1998; Kitano et al., 2002; Matsuki et al., 2003; Metzger et al., 2004; Khovidhunkit et al., 2004; Yerkovich et al., 2004) probably due to the triggering of neuroendocrine responses given that IL-1 induces the release of CRF (Sapolsky et al., 1987), melanocortins and other neuropeptides (Tocci and Schmidt, 1997) as well as a direct effect on metabolic activity of different tissues such as skeletal muscle, liver and adipose tissue. IL-1 acts directly on lipid metabolism by inhibiting lipoprotein lipase activity, which control the availability of lipid fuel in the body (Beutler and Cerami, 1985; Doerrler et al., 1994; Matsuki et al., 2003) and decreasing intestinal lipid absorption and lipid accumulation (Argiles et al., 1989). Furthermore, this cytokines can modulate adipocyte function by suppressing the synthesis of fatty acid transport proteins in adipose tissue and the adipocyte maturation in vitro (Gregoire et al., 1992; Memon et al., 1998a). Using an IL-1ra-deficient (IL-1ra−/−) mice Matsuki et al. (2003) showed that excess IL-1 signaling suppresses weight gain and decreases fat mass without changes in food intake, but the morphology and cell volume of adipocytes is not altered compared with those of the wild-type (Fig. 19), as well as the hypothalamic expression of adiponectin, leptin and resistin or the expression levels of different anorectic and orexigenic hypothalamic feeding regulators but have impaired lipid storage and lipid uptake into adipose tissue, these defects being more accentuated in males than in females. Furthermore, the high IL-1 signaling causes a decrease in serum leptin, insulin and triacylglycerol, and but an enhancement of insulin sensitivity (Fig. 20).

There are some evidences that suggest the participation of IL-6 in the regulation of lipid metabolism. Thus, IL-6-deficient mice develop obesity along with obesity-related metabolic disorders and these alterations are partially abolished by exogenous IL-6 administration (Wallenius et al.,

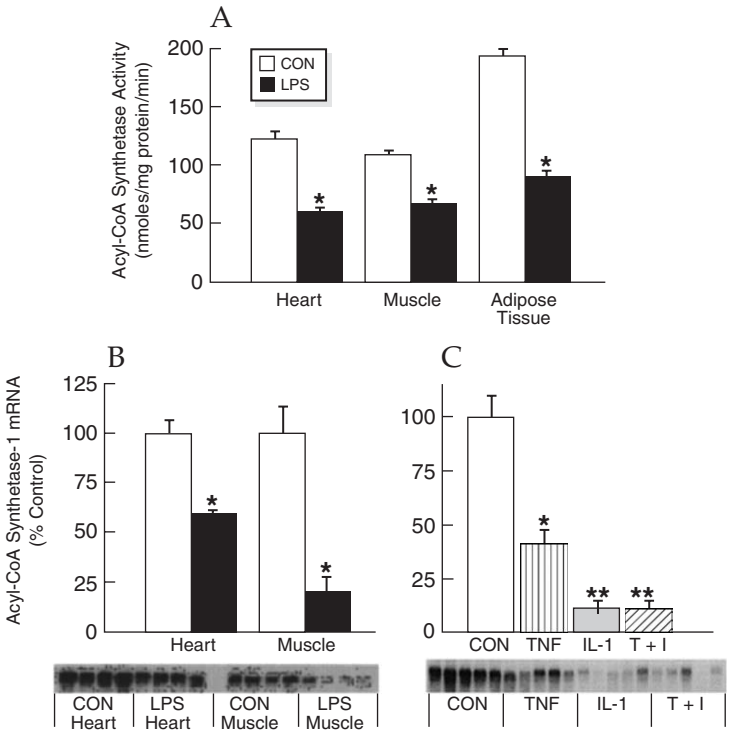

Fig. 18. (A) Effect of intraperitoneal lipopolysaccharide (LPS) on acylCoA synthetase 1 (ACS1) activity in adipose tissue, heart and muscle of Syrian hamsters. *$p<0.001$; (B) Effect of intraperitoneal lipopolysaccharide on ACS1 mRNA levels in heart and muscle. Values are means $\pm$ SEM. *$p<0.001$; (C) Effect of tumor necrosis factor (TNF), interleukin-1 (IL-1) and the combination of TNF and IL-1 (T 1 I) on ACS1 mRNA levels in liver of Syrian hamsters. *$p<0.002$, **$p<0.001$. (From Memon et al., 1998b).

2002a). Furthermore, it has been observed that intracerebroventricular administration of this cytokine acutely stimulate energy expenditure (Rothwell et al., 1991; Wallenius et al., 2002a) and decreases the weight of mesenteric and retroperitoneal fat pads and circulating leptin levels (Wallenius et al., 2002b; Fig. 21). Also in mice bearing an IL-6-secreting tumor for 18 days a reduction in body fat is observed (Metzger et al., 2001). In healthy humans, a negative correlation between IL-6 cerebrospinal fluid levels and total body weight, subcutaneous and total body fat and serum leptin (Stenlof et al., 2003). Ciliary neurotrophic factor, which is structurally related to IL-6, has been shown to reduce body fat in mice fed with diet-induced obesity (Gloaguen et al., 1997; Lambert et al., 2001) and also affect protein metabolism by inducing protein degradation (Espat et al., 1996).

The efferent signals of acute phase response and the interaction between immune system and hypothalamus–pituitary–thyroid axis play an important role because of the effects of the thyroid hormones on metabolism. Immune-derived cytokines, mainly pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6, stimulate the growth and the function of thyroid cells (Armstrong and Klein, 2001). It has been observed that serum thyroid-stimulating hormone concentrations decreases during 5 h following a single injection of IL-1β (Dubuis et al., 1988) followed by a decline in total tetra-iodothyronine and an increase in free tetra-iodothyronine in rats (Wang et al., 1998). Similar results have been reported after continuous infusion of TNF-α, IL-1β and IL-6 in rats (Hermus et al., 1992; Sweep et al., 1992).

Other peripheral mechanisms of cytokines may be the enhancement of the availability of tryptophan (the 5-HT precursor) to maintain

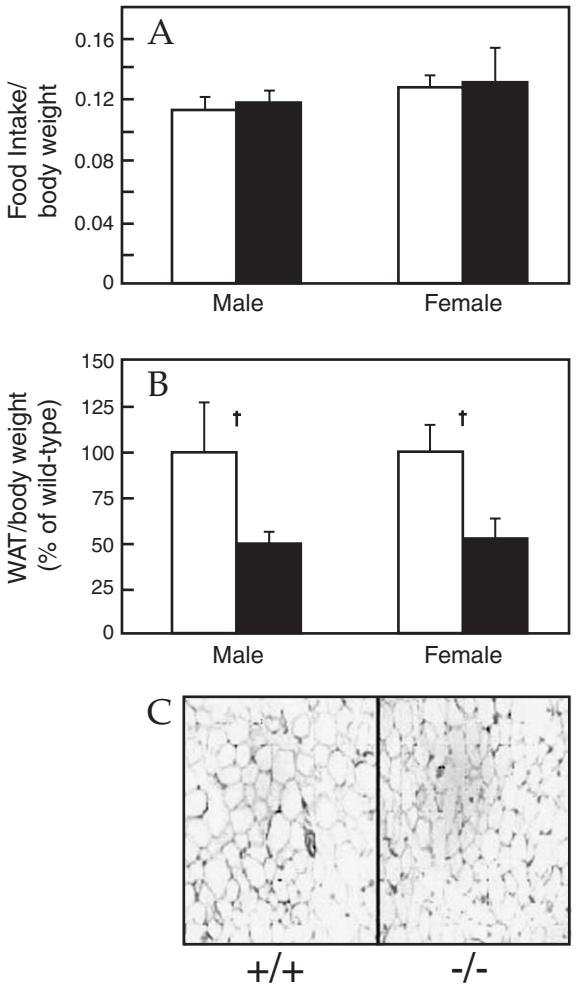

Fig. 19. Using a IL-1ra-deficient (IL-1ra−/−) mice it has been shown that excess IL-1 signaling suppress weight gain and decrease fat mass without changes in food intake, but the morphology and cell volume of adipocytes is not altered compared with those of wild type. (A) Food intake per body weight, (B) white adipose tissue (WAT) weight per body weight and (C) Paraffin sections of WAT from epididymal fat pads in IL-1Ra−/− mice. IL-1Ra−/− (shaded bars, −/−) and wild-type (white bars, +/+) mice and IL-1Ra−/−. Data are expressed as the mean±SEM. *$p<0.05$, † and $p<0.01$ vs. wild-type mice. (From Matsuki et al., 2003).

an elevated 5-HT turnover (Dunn, 1992) given that brain 5-HT synthesis depends on the brain availability of this amino acid (Schaechter and Wurtman, 1990) which is positively correlated to plasma-free tryptophan concentration (Fernstrom and Wurtman, 1972). In different anorexia animal models (Kurzer et al., 1988; Meguid et al., 1992; Muscaritoli et al., 1996; Laviano et al., 1999) and anorectic patients with different diseases (Cangiano et al., 1994; Laviano et al., 1997; Aguilera et al., 2000) an increase in plasma and brain free tryptophan concentrations and brain serotoninergic activity has been reported suggesting a connection between anorexia disease, circulating tryptophan, brain serotoninergic activity and cytokines. Moreover, in anorectic tumor-bearing rats, enhanced free tryptophan circulating levels decrease to normal levels after tumor removal thereby improving food intake (Cangiano et al., 1994). The subcutaneous administration of IL-1α to normal rats during 2 days caused a rise in plasma-free tryptophan associated to a decrease of food intake and subsequently to a reduction in carcass adiposity and body weight (Sato et al., 2003; Fig. 22). Although the injection of tryptophan increases plasma free and total tryptophan there was not a clear effect on food intake. This lack of effect may be due to the newly synthesized 5-HT in the hypothalamus that is not released (Schaechter and Wurtman, 1990). Moreover, the neuronal activity is a decisive factor to hypothalamic 5-HT release, and IL-1α is able to modulate neuronal activity (Bartholomew and Hoffman, 1993). Insulin may contribute to the anorectic effect of IL-1α taking into account that circulating insulin increases after cytokine injection and that there is a negative correlation between food intake and plasma insulin (Sato et al., 2003). It is known that peripheral insulin increase plasma tryptophan and decreases other neutral amino acids (Fernstrom and Wurtman, 1972) that compete with free tryptophan for brain entry (Fernstrom and wurtman, 1972; Landel et al., 1987) leading to an enhanced availability of hypothalamic tryptophan and subsequently to a rise in 5-HT production that may be released after the increase in neuronal activity induced by IL-1α.

Purpose

As we have mentioned above, during infectious disease, trauma or cancer process, host respond with a generalized defense reaction called *acute*

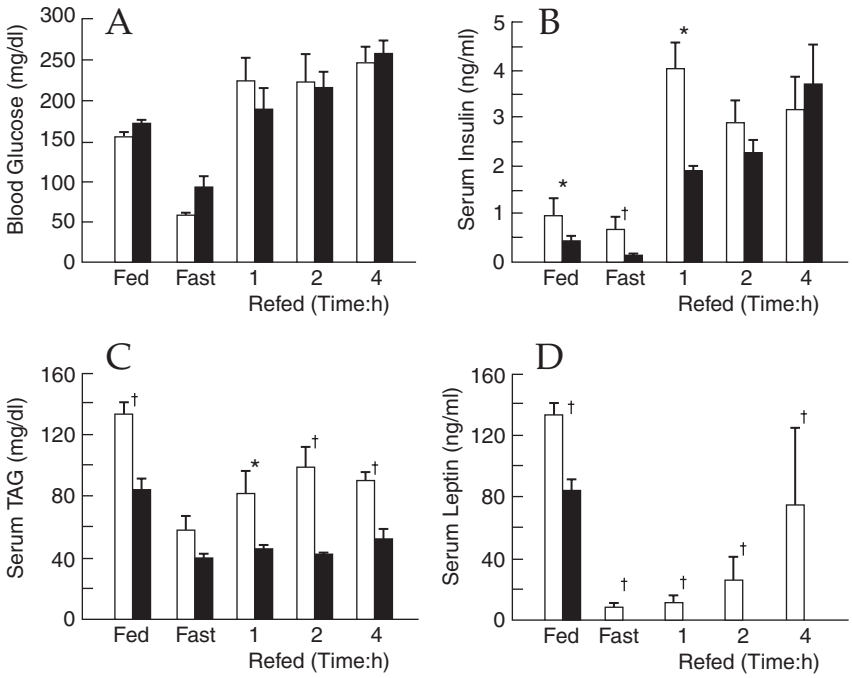

Fig. 20. Decreased serum levels of insulin, triacylglycerol (TAG), and leptin in IL-1Ra−/− mice. (A) Blood glucose, (B) serum insulin, (C) TAG and (D) leptin levels in body weight-matched wild-type (white bars) and IL-1Ra−/− (shaded bars) mice. Data are expressed as the mean ± SEM. *$p<0.05$, †, $p<0.01$ vs. wild-type mice. (From Matsuki et al., 2003).

phase response which is characterized by alterations in immune, metabolic, endocrine and neural functions as well as behavior (Baumann and Gauldie, 1994) aimed to inhibit the proliferation and spread of the pathogens. These behavioral alterations, such as fever, somnolence, lethargy or anorexia, called "sickness behavior" (Hart, 1990) are mediated by cytokines and are adaptive and beneficial for the host at least during the first phases of infectious or trauma process (Hart, 1988, 1990). For instance, anorexia reduces the energy expenditure due to search for food and decrease the growth of the pathogenic agents by reducing the availability of nutrients coming from food such as free iron, which is indispensable for bacterial proliferation (Weinberg, 1984). However, although these modifications are an essential part in response to different challenges, excessive or long-term production of cytokines or synthesis of cytokines in incorrect biological context compromises host survival and are associated with pathology and mortality in many different diseases. For example, prolonged changes in structure and function of lipoproteins may contribute to atherogenesis (Khovidhunkit et al., 2004). Therefore, potentially beneficial immunotherapies based on long-term cytokines administration cannot be applied because of these harmful side effects, particularly in the CNS (Smith et al., 1990).

Therapy to reverse acute effects of cytokines on acute phase response

Cytokine metabolism and actions can be modulated not only by pharmacological procedures but also by nutrients. There are some evidences that strongly suggest a role of dietary factors in the regulation of cytokines production (Sasaki et al., 1999; Das et al., 2003; Sato et al., 2003). In particular, it has been observed that diets rich in long-chain ω-3 polyunsaturated fatty acids, such as eicosapentaenoic acid or docosahexaenoic acid inhibits the production of IL-1 and TNF-α

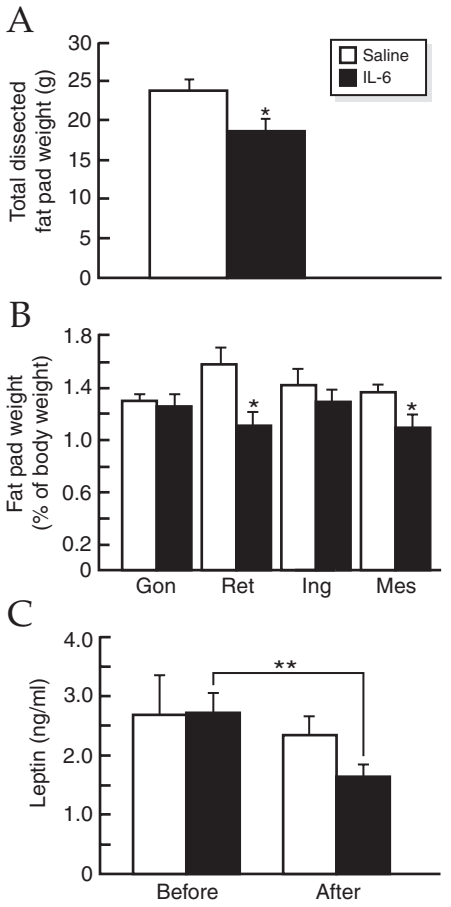

Fig. 21. Dissected fat pads and serum leptin. Three intraabdominal fat pads (gonadal (Gon), retroperitoneal (Ret) and mesenteric (Mes)) and the inguinal (Ing) fat pad (a subcutaneous fat pad in the groin) were dissected. (A) The total weight of the dissected fat pads after two weeks of intracerebroventricular treatment with saline or IL-6 (0.41 g/day). (B) Comparison between the relative weights of the different dissected fat pads (% of body weight) after saline and IL-6 treatment. (C) Leptin levels before and after 2 weeks of intracerebroventricular treatment with saline or IL-6 treatment. (A,B) *$p<0{:}05$, vs. control, (C) **$p<0{:}01$ vs. before IL-6 treatment. (From Wallenius et al., 2002b).

(Endres et al., 1989; Sasaki et al., 1999) as well as reduces its biological activity, and more specifically those related to food intake (Sato et al., 2003). Further, experimental and clinical studies with cancer patients have shown a reduction of weight loss when the diet was enriched with ω-3 fatty acids from fish oil (Dagnelie et al., 1994;

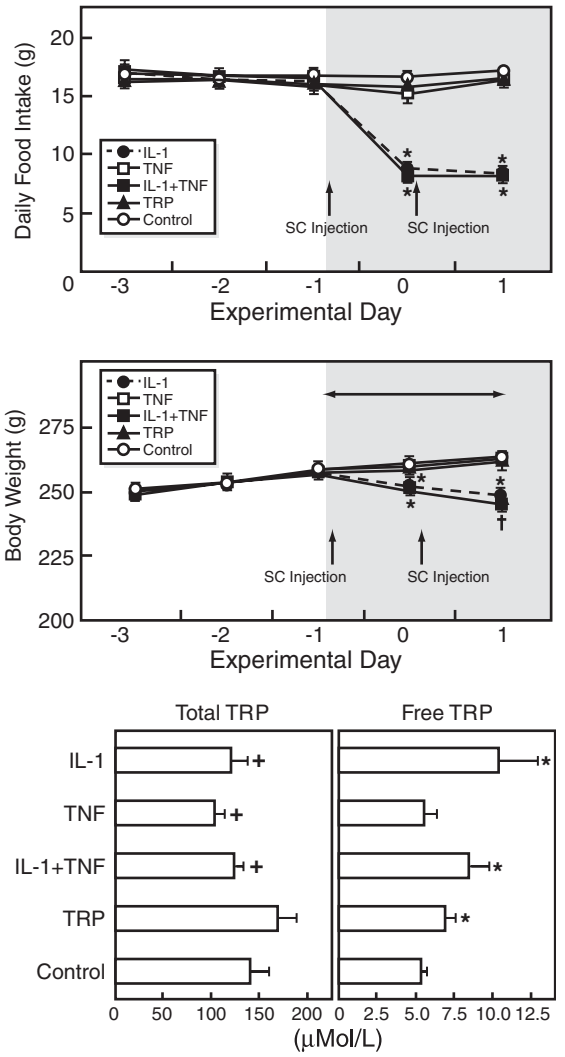

Fig. 22. (A) Daily food intake before and after subcutaneous injections of cytokines or tryptophan. The shaded area indicates the period influenced by the injections. *$p<0.005$ vs. the TNF, TRP and control groups. (B) Body weight before and after subcutaneous injections of cytokines or tryptophan. Before injections, there was no significant difference in body weight among the five groups. The asterisks indicate that the changes in body weight in the IL-1 and IL-1 + TNF groups were significantly different vs the other three groups, and, furthermore, that the change in the IL-1 + TNF group was greater than that of the IL-1 group. * $p<0.05$ vs. the TNF, TRP and control groups. (C) Plasma-total and -free tryptophan among the five groups. *$p<0.05$ vs. the control group. + $p<0.05$ vs. the TRP group. # $p<0.05$ vs. the TNF, TRP and control groups. The data were mean ± SEM. (From Sato et al., 2003).

Barber et al., 1999). Moreover in tumor-bearing rats, diets rich in eicosapentaenoic acid diminish tumor growth and ameliorate cachexia (Jho et al., 2002). A marked improvement in food intake, and its two components, body weight and tumor progression in methylcholanthrene tumor-bearing rats fed with ω-3 fatty acids-supplemented diet compared with tumor-bearing rats fed with chow diet are reported (Ramos et al., 2004b; Fig. 23). This diet retarded the appearance of the tumor and reduced its size and weight as it has been described previously (Bartoli et al., 1993; Dagnelie et al., 1994; Chen and Istfan, 2000) and avoided the decrease in both meal size and meal number at the onset of anorexia and in body weight resulting in no difference between tumor-bearing rats fed with ω-3 fatty acids-enriched diet and control groups. The effects of ω-3 fatty acids on the progression of the tumor may be mediated by the inhibition of smooth cells proliferation and the subsequent reduction of vascularization of the tumor (Kremer and Robinson, 1991; Rose et al., 1991). The ω-3 fatty acids sustain food intake during tumor growth by means of maintaining both meal number and meal size, delaying the onset of anorexia and thus preventing body weight loss. It is likely that the inhibition of TNF-α and IL-1 and leukotriene B4, which enhance IL-1 production, exerted by ω-3 fatty acids (Kunkel and Chensue, 1985; Rola-Pleszczynski and Lemaire, 1985) as well as the inhibition of mononuclear cell proliferation (Meguid and Pichard, 2003) be responsible for the beneficial effects of these fatty acids on food intake. This assumption is supported by the fact that the ARC expression of TNF-α and IL-1 in tumor-bearing rats fed with diet rich in ω-3 fatty acids was lower than in tumor-bearing rats fed with chow diet (Ramos et al., 2004b). Furthermore, we found an increase in ARC and PVN NPY expression in tumor-bearing rats fed with ω-3 fatty acids supplemented diet, measured by mean of microarray analysis. We also reported increased levels of NPY immunoreactivity in ARC and magnocellular division of PVH, but not in parvocellular PVH or SON, and decreased levels of α-MSH in magnocellular PVN and ARC, but not in parvocellular section of PVN, as well as a decrease in immunoreactivity of 5-HT_{1B} receptor

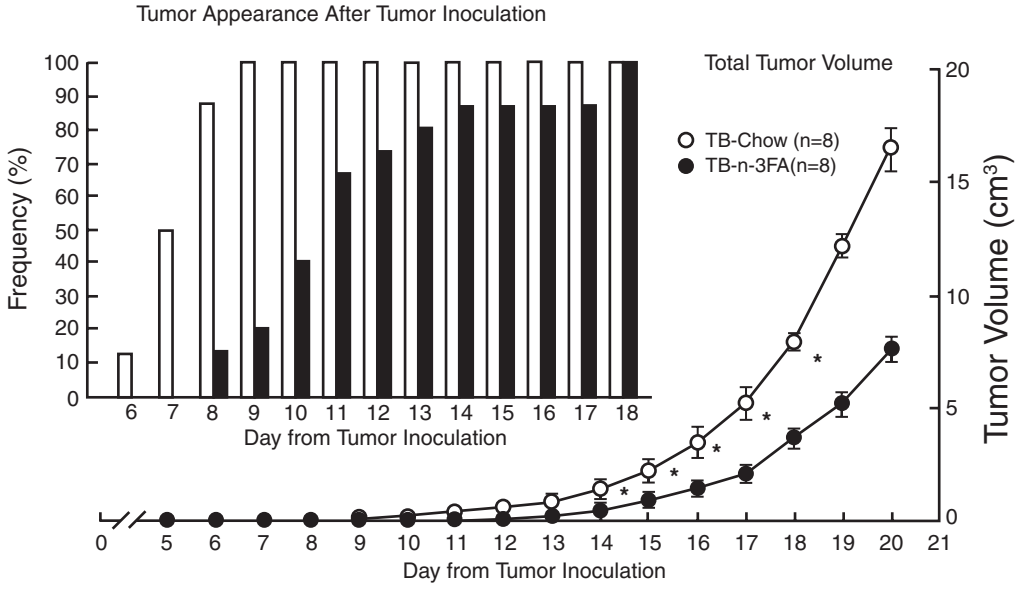

Fig. 23. Tumor appearance and changes of volume in tumor-bearing (TB) rats. Tumor appearance occurred in 100% (8 of 8) within 9 days after tumor inoculation in tumor-bearing Chow rats; in tumor-bearing ω-3 fatty acids rats, tumor appearance occurred in 20% (2 of 8) within 9 days and in 100% (8 of 8) on day 18 after tumor inoculation. *$p \rangle \lambda\tau \sim 0.05$ vs. tumor-bearing ω-3 fatty acids rats. FA, fatty acid. (From Ramos et al., 2004b).

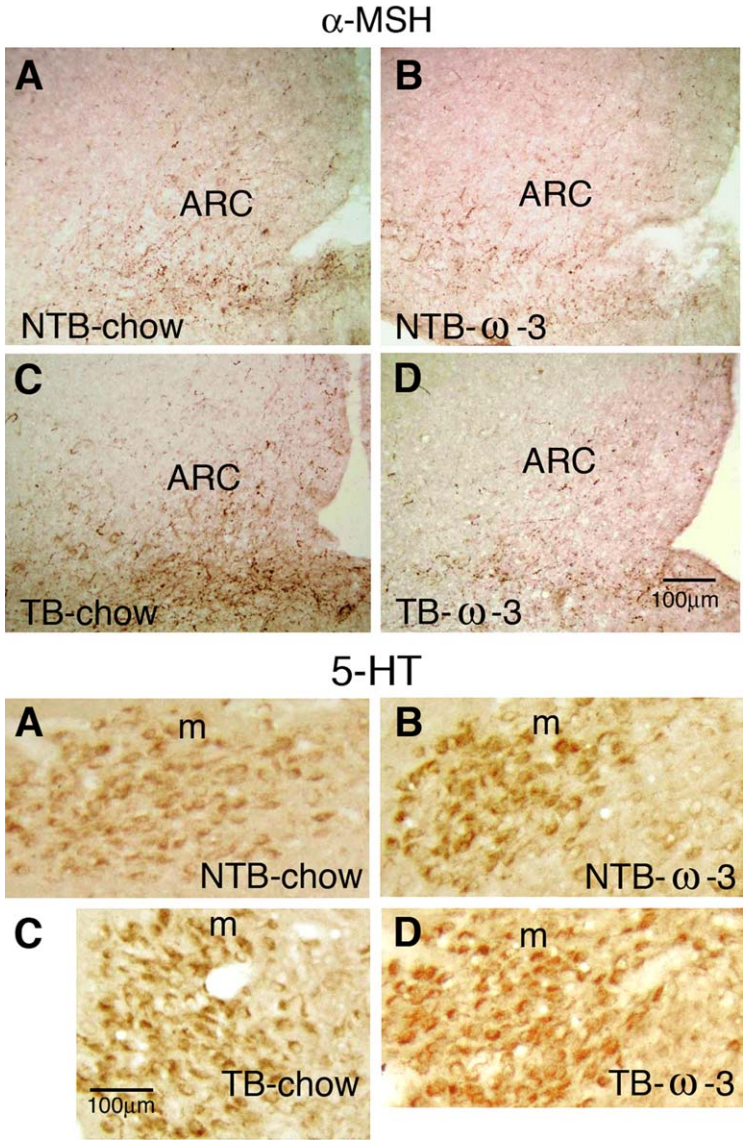

Fig. 24. α-MSH immunoreactivity in ARC (top). In non tumor-bearing rats (panels A and B), ω-3 fatty acids-supplemented diet did not influence α-MSH immunoreactivity. Following tumor injection, an increased expression of α-MSH occurred in tumor-bearing Chow (panel C). The use of a ω-3 fatty acids supplemented diet prevented the increase of α-MSH immunoreactivity in tumor-bearing ω-3 fatty acids rats (panel D). This was demonstrated by the less intense immunoreactivity (64% lower) in tumor-bearing ω-3 fatty acids vs. tumor-bearing Chow. 5-HT_{1B}-receptor immunoreactivity in magnocellular PVN (mPVN, bottom). Serotonin is anorexigenic and therefore, 5-HT_{1B}-receptors should be upregulated after tumor inoculation. This figure shows that, after tumor inoculation, the increase in 5-HT_{1B}-receptors was less pronounced in rats fed a ω- 3 fatty acids supplemented diet vs. rats fed chow (panels D vs. C). In tumor-bearing Chow vs. non-tumor-bearing Chow (panel C vs. A), there was an increase of 40% in 5-HT1B-receptor immunoreactivity ($p<0.05$), while in tumor-bearing ω-3 fatty acids vs. non tumor-bearing ω-3 fatty acids (panels D vs. B), a nonsignificant increase of 14% occurred, demonstrating that the ω-3 fatty acids supplemented diet prevented the upregulation of 5-HT_{1B}-receptors. Scale bar = 100 μm. V, ventricle. (From Ramos et al., 2005.)

in SON (Ramos et al., 2005; Fig. 24). The ω-3 fatty acids mechanism(s) of action is/are not completely known. It has been proposed that ω-3 fatty acids may affect the neuronal membrane by inhibiting the production of eicosanoids, which are lipid-derived modulators and among them arachidonic acid is the most important of their precursors. This action alters the phospholipids composition of cellular membrane leading to the alteration of different membrane functions, such as those related to neurotransmitter receptors, second messenger and transport proteins (Meterissian et al., 1995). On the other hand, this inhibition not only affects numerous biological responses but also modulates neurotransmission via inhibition of metabolism and actions of arachidonic acid and its derivatives (Bazan et al., 1997). These data suggest that the effects of ω-3 fatty acids on food intake may be mediated by the modulation of the balance of hypothalamic orexigenic and anorectic factors via inhibition of cytokines production. Further, these data point out the possibility of the therapeutic use of the ω-3 fatty acids at earlier stages of tumor progression for preventing body weight loss and ameliorating anorexia as well as for inhibiting tumor growth.

To this emerging therapy may now be added the idea of the use of nicotine in a sociably acceptable manner, and preliminary studies in our laboratory in tumor-bearing rats show promising results (Personal observations, Laviano and Meguid, 2005).

Abbreviations

ACTH	adrenocorticotropin hormone
AP	anterior pituitary
ARC	arcuate nucleus
DA	dopamine
CRF	Corticotropin-releasing factor
HPA	hypothalamus–pituitary–adrenal
5-HT	serotonin
IL	interleukin
IL-1ra	interleukin-1α receptor antagonist
IL-1RI	IL-1 receptor type I
IL-1RAP	interleukin-1 receptor accessory protein
INT-γ	interferon gamma
LHA	lateral hypothalamic area
NPY	neuropeptide Y
POMC	pro-opiomelanocortin
PVN	paraventricular nucleus
SCN	suprachiasmatic nucleus
SON	supraoptic nucleus
TNF-α	tumor necrosis factor-α
VMH	ventromedial hypothalamus

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