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Perinatal malnutrition and the protective role of the physical training on the immune system

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Abstract

Developing organisms have the ability to cope with environmental demands through physiologic and morphologic adaptations. Early life malnutrition has been recognized as an environmental stimulus that is related with down-regulation of immune responses. Some of these effects are explained by the epigenetics and the programming of hormones and cytokines impairing the modulation of the immune cells in response to environmental stimuli. Recently, it has been demonstrated that these effects are not deterministic and current environment, such as physical activity, can positively influence the immune system. Here, we discuss the effects of perinatal malnutrition on the immune system and how it can be modulated by physical training. The mechanism includes the normalization of some hormones concentrations related to growth and metabolism such as leptin, IGF-1 and glucocorticoids.

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LA DESNUTRICIÓN PERINATAL Y EL PAPEL PROTECTOR DEL ENTRENAMIENTO FÍSICO EN EL SISTEMA INMUNOLÓGICO

Resumen

Los organismos en desarrollo tienen la capacidad de hacer frente a las demandas ambientales a través de adaptaciones fisiológicas y morfológicas. la malnutrición perinatal ha sido reconocida como un estímulo ambiental que está relacionado con la baja regulación de la respuesta inmune. Algunos de estos efectos se explican por la epigenética y la programación de las hormonas y citoquinas que son responsables de la modulación de las células inmunes en respuesta a los estímulos ambientales. Recientemente se ha demostrado que estos efectos no son deterministas y que la actividad física puede influir positivamente en el sistema inmunológico. Aquí se discuten los efectos de la desnutrición perinatal sobre el sistema inmune y cómo puede ser modulada por el entrenamiento físico. El mecanismo incluye la normalización de las concentraciones de algunas hormonas relacionadas con el crecimiento y el metabolismo tales como la leptina, IGF-1 y los glucocorticoides.

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Palabras-clave: *Actividad física. Plasticidad fenotípica. Respuesta inmune. Plasticidad del desarrollo. Hormona.*

Introduction

The development of the immune system occurs in the beginning of gestation period in both human and animals[1]. During the development, stem immune cells migrate from primitive site of differentiation as the liver and endothelium through bone marrow in order to advance the process of maturation[2]. The interaction between mother and fetus via placenta is important in order to keep fetus under a strict condition of development. This interaction includes hormonal environment, blood exchange, oxygen and nutrients availability[3]. In addition, the critical period of development of the immune system also occurs during lactation and the first infancy[4]. Glucose and amino acids

are the main nutrients for the normal development of fetus during pregnancy. During lactation, fatty acids assume a similar importance for normal development of suckling offspring[5].

Adverse nutritional availability during perinatal life can increase the individual's susceptibility to adulthood metabolic disease[6-8]. Metabolic diseases are classified as inflammatory disorders because they are accompanied by elevated concentrations of proinflammatory cytokines such as IL-1, IL-6, and TNF-α, as well as increased concentrations of glucocorticoids[9]. Recently, it has been recognized that mother's nutrition from conception through lactation may program the structure and/or function of the immune system by permanently altering specific cell populations with a last impact on the development of immune response and high susceptibility to infection and allergy[10-12]. The mechanisms by which maternal malnutrition may exert an influence on the emerging immune system include the phenotypic plasticity that explain how environmental stimuli influence the expression of a phenotype characteristic from a single genotype[13]. In addition, there is a crosstalk between the immune system and the neuroendocrine system, epigenetic alterations as DNA methylation, histone acetylation and microRNA expression of immune mediators and hormones[14].

The postnatal environment such as lifestyle (diet and exercise) play an important role in the programming the offspring's susceptibility to disease[15-17]. It has been well established that regular physical training enhances the cell-mediated immunity, phagocytosis, migration of neutrophils to the infection, cytokine production and increased lymphocyte function[18-20]. For example, moderate physical exercise (75% VO_2max, 5 times week, during 8 weeks) increased the percentage of TCD4 lymphocytes in blood and thymus and attenuated the rate of lymphocytes apoptosis in adult rats submitted to acute restraint stress[21].

It is reasonable to consider that this kind of stimuli can induce positive adaptations on immune system even though the system was programmed to develop early disease or more susceptible immunity. Indeed, our previous studies showed that moderate physical training attenuated the effects of perinatal low-protein diet on the secretion of leptin by visceral adipose tissue, the phenotype of skeletal muscle fiber and the morphology of the spleen in adult offspring submitted to perinatal low-protein diet[15-17]. The underlying mechanism included the normalization of some hormones concentration such as leptin, IGF-1 and glucocorticoids that were programmed by perinatal malnutrition[9,22].

The present paper will discuss the effects of perinatal malnutrition with emphasis on the imprinting factors and mechanisms acting during gestation and lactation that can predispose the immune system to early impairment. Furthermore, we will discuss about the effects of physical training by attenuation or restoring the long-last effects of early life adverse nutrition. Finally, we highlight the probable underlying mechanisms including cytokines and hormones actions.

The development of the immune system in response to nutritional stimuli

Malnutrition (undernutrition or overnutrition) has been recognized as an environmental stimulus that is related with down-regulation of some immune responses[23]. In low and middle income countries, children mortality under 5 years old reached more than 8.7 million of deaths, where 68% were due to infectious diseases like pneumonia, diarrhea and malaria[24]. These infants suffered with re-incident infection because of early state of undernutrition[25]. Furthermore, maternal overnutrition was associated with high inflammatory state in children under 5 years old[26, 27].

In rats, previous studies have shown that maternal low-protein diet (9.5% casein during gestation and lactation) is related to peritoneal macrophages impaired spreading, phagocytosis and microbicide functions[23]. Maternal free-protein diet is also responsible for inhibited leukocyte bone marrow mobilization and migration of neutrophils under stimulation of *Carrageenan* in offspring at 60th day of life[28, 29]. Maternal overnutrition (high-fat diet during gestation and lactation) was related to up-regulation of proinflammatory pathway, especially of genes related to inflammatory response and cytokine signaling in rat offspring (12 months of age)[30]. Table I shows the list of studies that evaluated the association between maternal malnutrition and the consequences for the immune system of the offspring.

The underlying mechanisms for the short and long-term effects of malnutrition on the immune system can be explained by the phenotypic plasticity. This biological phenomenon was firstly used to explain how environmental stimuli influence the expression of a phenotype characteristic from a single genotype[13]. In addition, epigenetic alterations as DNA methylation, histone acetylation and microRNA expression can explain how an organism can adapt to environmental stimulus during the critical period of development and the association with consequences during the lifespan[14]. For example, perinatal undernutrition is related to down-regulation of leptin gene expression in adult mice, and leptin participates in the effector T lymphocytes activation[31, 32]. The maternal overnutrition is associated with the methylation of offspring genes that express the IL-8, B-lymphocyte receptor and glucocorticoids receptor signaling pathways[33]. The methylation of some genes from the IL-8 pathway is related to the plasma C-reactive protein expression[33].

Malnutrition during the critical period of development can alter the development of immune system

Table I
Early-life malnutrition effects on offspring immune cells (2010 to 2014)

Cells	*Species*	*Model of Malnutrition*	*Period of Malnutrition*	*Age of evaluation (offspring)*	*Effects*	*References*
Bone marrow macrophages	Sprague-Dawley rats	50% restriction diet	Gestation	160 days	↑Serum TNF-α and IL-1β; ↑Production of IL-6, IL-1β and IL-10 after LPS (supernatant); TNF-α wasn't altered; ↑M1 phenotype marker CD11c, and ↓M2 phenotype marker PPAR-γ	58
Thymocytes and Splenocytes	Wistar rats	8% protein diet vs 22% protein diet	Gestation and lactation	30 days	Thymocytes:↓Double positive cells; ↑CD4+; ↑CD8+; ↑ObR protein expression; ↓apoptosis (AnnexinV); Proliferation: N/A ↑Bcl2; ↓Bax; ↑Nuclear NF-kB p65; ↓IkB; Splenocytes: N/A surface markers	59
Thymus and Spleen Lymphocytes	CD1 Mice	6% protein diet vs 24% protein diet	Gestation and lactation	2, 7, 14 and 21 days	↑Serum eotaxin Thymus: ↓total cell number Spleen: ↓total cell number ↓Spleen mass ↑CD4+/CD8+ ↑CD8+	60
Peripheral blood mononuclear cells (PBMC)	German Landrace Pigs	6.5% protein diet vs 12.1% protein diet (adequate) vs 30% protein diet	Gestation	1, 27, 80 and 180 days	Serum: ↓IgA (day 1) ↑IL-10 (day 47) ↑IL-6 (day 47) Before vs after weaning: ↓Lymphocytes proliferation 30%: Serum: ↓imunoglobulins (IgG, IgM and IgA) (day 1) Before vs after weaning: ↑CD4+ ↑CD4/CD8 ↓Lymphocytes proliferation	61
Bronchoalveolar lavage (BAL) lymphocytes, eosinophils and neutrophils	Wistar rats	50% restriction diet	Gestation	60 days	BAL: ↓total lymphocytes counts ↓CD4+ ↓eosinophils and neutrophils migration ↑TNF-a ↓IL-6 Lung Tissue: ↑IFN-g ↓IL-4	62

Table I (cont.)
Early-life malnutrition effects on offspring immune cells (2010 to 2014)

Cells	*Species*	*Model of Malnutrition*	*Period of Malnutrition*	*Age of evaluation (offspring)*	*Effects*	*References*
Spleen and mesenteric T cells	C57BL/6J Mice	0.6% low protein diet vs control	19 to 33 days of age	22 and 33 day (third and 14th day of experimental diet)	↓Serum IL-10	63
T lymphocytes	Sprague-Dawley rats	50% restriction diet	Gestation and lactation	8-9 weeks	↓WBC; ↓Lymphocytes; ↓CD4+; ↓CD8+; ↑CD4/CD8; Serum: ↓IL-2; IL-7. ↓Actin polimerization; ↓Proliferation; T cells: ↓IL-2;IFN-γ.	64
Blood neutrophils	Wistar rats	Protein-free diet vs 22% protein diet	First 10 days of lactation	50 to 60 days	↓Leukocyte migration ↓Leukocyte blood pool ↑Superoxide production ↑Nitric oxide production ↑iNOS expression ↑NF-kB ↓IkB ↑TNF-α (serum)	27
Thymus	C57/B16 Mice	8% protein diet vs 20% protein diet	Gestation or lactation	21 days or 12 weeks	Gestation: ↑PCNA (21 days) ↓PCNA (12 weeks) ↑SIRT1 (21 days) ↑p53 (both ages) ↑IL-7 expression (21 days) ↑IL-7R expression (21 days) Lactation: ↑Thymus relative weight (12 weeks) ↑PCNA (both ages) ↑ SIRT1 (both ages)	65
Splenocytes	C57BL/6J Mice	29% lard (High fat) diet vs control	Gestation and lactation; gestation; or lactation	20 weeks	Lactation: ↓ Thymus and Spleen relative weight ↓IgG Gestation: ↓Thymus cortex thickness ↓Splenocytes total number ↑Serum TNF-a ↓IgG ↑IgE	66
Kidney Macrophages	Sprague-Dawley Rats	45% fat (High fat) diet + 10% fructose drinking water vs control	Gestation and lactation; gestation; or lactation	17 weeks	↑TGF-b ↑CD68+ on kidney tissue	67

Table I (cont.)
Early-life malnutrition effects on offspring immune cells (2010 to 2014)

Cells	*Species*	*Model of Malnutrition*	*Period of Malnutrition*	*Age of evaluation (offspring)*	*Effects*	*References*
Peritoneal macrophages; Splenocytes and Colon tissue	BALB/c and C57BL/6Mice	Western diet -WD (40% fat) or control diet (10% fat)	Gestation and lactation	5 to 6 weeks	After skin infection, WD offspring developed larger abcesses with higher bacteria number; Skin: ↓IL1-β; ↓TLR2; ↓IL17A; ↓IL-10; ↓β-defensin 4 Colon: ↑IL-6; ↑IL-1β; ↑IL17; ↓TRegs. Spleen: ↓TNF-α; ↓IL-6; ↓TReg Macrophage: ↓TLR4; ↓LBP	68

TNF-α - tumor necrosis factor alpha; IL-1β - interleukin-1 beta; IL-6 – interleukin-6; IL-10 – interleukin-10; LPS – lipopolysaccharide; CD11c – cluster differentiation 11c; PPAR-γ - peroxisome proliferator-activated receptor-γ; CD4 – cluster differentiation 4; CD8 – cluster differentiation 8; ObR – obesity receptor; Bcl2 – B cell lymphoma-2; Bax – BcL2 associated protein; NF-kB - nuclear factor-kB; IkB – inhibitor of NF-kB; IL-10 – interleukin-10; IgA – immunoglobulin A; IL-6 – interleukin-6; IFN-γ - interferon-γ; IL-4 – interleukin-4; WBC – white blood cells; IL-7 – interleukin-7; iNOS – inducible nitric oxide synthase PCNA – proliferating-cell nuclear antigen; SIRT1 – silent information regulator 1; LBP – lipid binding protein; IL-7R – interleukin-7 receptor; IgG – immunoglobulin G; IgE – immunoglobulin E; TGF-β – tumor growth factor-β; CD68 – cluster differentiation 68; TLR2 – toll-like receptor 2; TRegs – regulatory T cells; TLR4 – toll-like receptor 4; LBP – LPS binding protein.

with long-last consequences by a mechanism that includes epigenetic adaptations[31]. However, these effects are not deterministic and current environmental stimuli can also induce phenotypic plasticity. For example, regular physical activity has been associated with positive effects to immune system[18,34,35]. It plausible to consider that this kind of stimuli can induce positive adaptations on immune system even though the system was programmed to develop early disease or more susceptible immunity.

Immunological adaptations to the physical training

It has been well known that regular physical exercise can induce immune adaptations, but these effects are dependent on the magnitude of the effort[36]. Physical exercise can be classified according to intensity (light, moderate or intense), frequency (number of sessions per week), type (anaerobic or aerobic) and duration (short or long)[37]. According to the American College of Sports Medicine (2011), a regular (at least three times a week), moderate physical exercise (50 – 75% VO_2max) is associated with benefits for health[38]. For the immune system, moderate physical training enhanced macrophage phagocytosis and oxidative burst, neutrophils oxidative burst, high percentage of TCD4 lymphocytes and cytokines production[18-20]. For example, moderate physical exercise (75% VO_2max, 5 times week, during 8 weeks) increased the percentage of TCD4 lymphocytes in blood and thymus and attenuated the rate of lymphocytes apoptosis in adult rats submitted to acute restraint stress[21]. Table II shows some examples of studies that evaluated the immune response to moderate physical training.

The underlying mechanisms can be related to the neuro-endocrine-immuno modulation in response to a repeated boat of exercise-induced stress[39]. In response to acute exercise, the neuroendocrine mediators are activated by both sympathetic nervous system (SNS) and hypothalamus-pituitary-adrenal (HPA) axis. The initial response includes the increase of noradrenalin and dopamine concentration in the central nervous system that activates immediately the release of adrenalin from adrenal medulla. Then, there is an increase of corticotrophin-release-hormone (CRH) from the hypothalamus that activates the release of adrenocorticotrophic hormone (ACTH) from intermediary zone of the pituitary. The ACTH will activate the cells from the adrenal cortex to release glucocorticoids[40-42]. Immune cells present adrenergic receptors (α and β) that are responsive to the increase of blood noradrenalin, adrenalin and beta-endorphins[43, 44]. Similarly, immune cells present receptors for glucocorticoids (RG) that are over-expressed in response to stress[45]. Immune cells can also produce and release cytokines that can modulate cells of neuro-endocrine system as

Table II
Effects of moderate physical training on immune system (2010 to 2014)

Immune Parameters	*Model*	*Type of training*	*Effect*	*Reference*
T cell CD4+ (TCD4)	Human (HIV positive men)	60-79% heart rate 45-60 min/d; 3 times/week; 8 weeks	↑TCD4+; Positive correlation between TCD4+ and $VO_{2\ max}$	58
Serum interleukins	Human (Systemic Lupus Erythematosus women)	Heart rate correspondent to the interval between the VAT and 10% below the rcp; 30-50 min/d; twice a week; 12 weeks	↓IL-10 Trend to ↓ TNF-α; ↓IL-6; ↓sTNFR1 and ↓sTNFR2	59
Blood CD4+ lymphocytes	Human (sedentary health man)	60% VO_2max; 30 min/d; 5 days/week; 5 weeks	↓Active caspase-3; ↓Phosphatidylserine externalization (apoptotic markers); ↓beclin-1; ↓Atg-1; ↓Lamp-2 (autophagic markers)	60
Blood lymphocytes; Neuronal and intestinal tissue	Swiss mice (*Trypanosoma cruzi* infected)	Light to mild effort; 30-45 min/d; 5 days/week; 8 weeks.	↓Total parasitemia; ↑Neuronal survival and hypertrophia; ↑Total thickness of intestinal wall; ↑Intraepitelial lymphocytes number; ↓Formation of inflammatory foci; ↑Serum TNF-α	61, 62
T and B lymphocytes	BALB/C	70% VO_2max; 60 min; 5 days/week; 11 weeks	↓Serum IL-4; ↓TNF-a; ↑B lymphocytes; ↑TCD4+;	63
T and B lymphocytes	Wistar rats	60% VO_2max; 1h/d; 5 days/week; 8 weeks	↑Proliferative capacity of T and B lymphocytes; ↑IL-2; ↑IL-4; ↑TNFR; ↑IL-2R; ↑IgG	64
	Wistar rats (Diabetes-induced)	60% VO_2max; 30 min/d; 6 days/week; 3 weeks	Serum: ↓TNF-α; ↓IL-6; ↓IL-1β; ↓CINC 2α/β; ↓C-reactive protein	65

HIV – human immunodeficiency virus; VO_2max – maximal oxygen consumption; IL-6- interleukin 6; IL-10 – interleukin-10; TNF-α – tumor necrosis factor alpha; sTNFR1 – soluble tumor necrosis factor α receptor 1; sTNFR2 – soluble tumor necrosis factor 2; VAT – ventilator anaerobic threshold; RCP – respiratory compensation point; Atg-1 – autophagy related 1; Lamp-2 - Lysosome-associated membrane protein 2; IL-2 – interleukin-2; IL-4 – interleukin-4; IL-1β – interleukin 1 beta; CINC 2α/β - cytokine-induced neutrophil chemotactic factor 2alpha/beta.

a bi-directional fashion. Immune cells can also produce and release hormone like ACTH.

Physical exercise is a model of physical stress that activates both SNS and HPA axis. For example, moderate physical exercise (55% VO_2max, 45 min) was associated with an increased expression of alpha-adrenergic receptors in neutrophils[46]. Previous studies have shown that in response to a long duration physical exercise, neutrophils are more responsible to the increase of blood beta-endorphin[47, 48]. Receptors for glucocorticoids are responsive for a regular physical exercise and immune cells present a down regulation that can be important for the process of inflammation[49].

Can physical training attenuate the effects of perinatal malnutrition?

Developing organisms have the ability to cope with environmental demands through physiologic and morphologic alterations[50]. The resulting phenotype can be continuously modulated by adaptive mechanisms of some tissues, like adipose tissue and skeletal mus-

cle. Perinatal malnutrition has been showed to affect the synthesis and action of hormones in the receptors. For example, GH-IGF-1 axis are affected by maternal protein restriction and adult offspring from low-protein mothers presented a lower GH mRNA expression, limiting growth by reducing hepatic IGF-1 synthesis[9]. Children born small for gestational-age showed altered GHRH-GHIGF1 axis and GH resistance[51,52].

Recently, it was described that there is an interaction between the IGF system and the inflammatory immune response[53]. For example, pigs with elevated IGF-1 expression presented a less increased expression of TNF-α while pigs with the high expression of IGFBP-3 presented elevated IL-6 expression[53]. It seems that there is an inverse association between the hepatic expression of the IGF system (IGF-1, IGFBP-3, GHR) and certain cytokines (IL-1β, IL-18, TNF-α) and acute-phase proteins[53]. Thus, the long-last effects of maternal malnutrition on the inflammatory response of immune cells can be related to the down-regulation of IGF-1 and GH-IGF1 axis. Physical exercise can modulate hormonal response and the GH/IGF-I system[54] by a mechanism that include inflammatory response and muscular repair[55]. In adult trained men submitted to a resistance exercise followed by cold water immersion, there was a IGF-mediated responses on slower-acting lymphocytes[55]. Our previous study showed that moderate physical training also reverted the profile of skeletal fibers toward oxidative phenotype in adult rats submitted to a perinatal low-protein diet by a mechanism that included high concentration of IGF-1[16].

Adipose tissue secretes a number of adipocytokines that are important in the metabolism and intrauterine growth. Leptin is one of the most important hormones secreted by adipocytes resembling proinflammatory cytokines (IL-6 and IL-12)[56]. It assumes an important role in regulating immune responses. For example, it has been shown that disease conditions of reduced leptin production are associated with increased infection susceptibility[56]. There is also a physiological role including the mediation of the nutritional status and immune competence[9]. Serum concentration of leptin is altered in adult offspring submitted to perinatal protein-restriction that was associated with leptin resistance, hyperleptinemia, accumulation of adipose tissue and inflammation as described in previous studies[9,57]. Our previous studies have shown that a perinatal low-protein diet induced an increased content of leptin on visceral adipose tissue of adult male rat offspring. These effects were attenuated by moderate physical training (70% VO_2max, 60 min/day, 5 days/week, 8 weeks). Thus, an important mechanism related to the immunomodulation of the physical training on adult subjects submitted to perinatal malnutrition is closely associated to the action of leptin.

Perinatal malnutrition during gestation or lactation is a stressful event that can activate the HPA axis by a mechanism that includes a permanent up-regulation of glucocorticoids receptors[22,58]. Pups (40-day-old) from food restricted mothers during gestation presented higher corticosteronemia and respond less to dexamethasone suppression than the controls[22]. Our previous study showed in endotoxemic rats that a protocol of moderate physical training reverted morphologic spleen alterations such as reduced number and size of lymphoid follicles and marginal zone area by a mechanism related to plasma corticosterone concentration[17]. Thus, current environmental stimuli, such as physical training, can modulate the neuroendocrine and metabolic status, which have direct impact on the immune system function[59]. It means that early life insults induce short-term adaptations but it does not means that this is deterministic since organs and physiological systems are constantly responsible to new environmental stimuli responding in terms of phenotypic plasticity[60].

Conclusions

Perinatal malnutrition has been recognized as an environmental stimulus that can alter the physiological developmental during a critical period of life. The immune system seems to be susceptible to perinatal malnutrition since it has been seen effects at short and long-term on the inflammatory response, synthesis of cytokines, down regulation of macrophages and monocytes, migration of neutrophils to infection and up-regulation of B-lymphocytes. The underlying mechanism includes the epigenetic influence enabling the animal to adapt to a lower nutrient supply by mutilation of DNA and acetylation of histones. However, in terms of phenotypic plasticity, the immune system can also respond as an adaptive fashion the current environmental stimuli like physical exercise. The mechanism includes the normalization of some hormones concentration related to growth and metabolism such as leptin, IGF-1 and glucocorticoids.

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