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Effects of Fetal Programming in the Inflammatory Response in Wistar Rats: A Systematic Review

Efectos de la Programación Fetal en la Respuesta Inflamatoria en Ratas Wistar: una Revisión Sistemática

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SUMMARY: The aim of this study was to review the literature on the effects of fetal programming in the inflammatory response in Wistar rats. A search was performed in the following databases: PubMed, MEDLINE, PUBMED, SCIENCE DIRECT, SCOPUS, LILACS, SpringerLink. The main search terms were malnutrition and inflammation in Portuguese and in English. Original articles were included involving albino rats and review articles were excluded involving humans or animals other than rats. Articles that were related to malnutrition which was not intrauterine and did not involve the concept of fetal programming were also excluded. Those items found in more than one database were counted only once. Sixteen articles were found in PUBMED, 16 in SCOPUS, 4 in MEDLINE, 341 in SCIENCE DIRECT, 8 in SciELO, 1 in LILACS and 77 in SPRINGERLINK totalling 463 articles from which 4 were selected for analysis after applying inclusion and exclusion criteria. Fetal programming seems to interfere with the inflammatory response in the adult offspring of Wistar rats, but its mechanisms remain uncertain.

KEY WORDS: Fetal Programming; Inflammation; Wistar Rats; Systematic review.

INTRODUCTION

Malnutrition is caused by quantitative and qualitative nutritional imbalances in the organism. These imbalances are mainly due to protein, fat and carbohydrate lack, which debilitate the organism physiological processes (Gurmini *et al.,* 2005).

Numerous epidemiological studies suggest that the intra-uterine environment is extremely important to determine the individual's future health (Dodic *et al*., 2002). The "fetal programming" concept suggests that the fetus may be programmed during the intrauterine maturing to develop diseases at an adult age (Vieau *et al*., 2007). According to this theory, alterations in the maternal nutritional state, reflected in the weight at birth, determine the development of diseases on adult phase (Bomfim & Lacerda, 2005; Landgraf *et al.*, 2008). The effects of intrauterine malnourishment depend on the development phase in which the fetus or organ is, the effects being as intense and permanent as precociously occurs the malnourishment and as later the nutritional recovery initiates (Gurmini *et al*.; Landgraf *et al*., 2008). Intrauterine malnutrition, even at different phases of gestation may affect the fetus by impairing the growth and development of various organs and systems. Studies with animals have been trying to correlate the nutrition state at the beginning of life and susceptibility to diseases on the adult phase, including diabetes mellitus, cardiovascular diseases, arterial hypertension and alterations to the circadian cycle (Kennaway *et al*., 2002).

The inflammatory process is fundamental to guarantee the organism integrity. It is the organism capability of responding to noxious stimuli, therefore maintaining the balance between the systems and the homeostasis. However, the benefits this process may be influenced by factors like malnourishment, genotype, pre-existent inflammation and chronic intoxication. Maternal malnutrition during gestation

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and lactation may result in endocrine immune dysfunction in the hypothalamic-pituitary-adrenal axis, permanently altering the adrenocorticotrophic and glucocorticoid hormones concentration, which promote changes in the leptin levels during acute and chronic inflammations, contributing affecting the endocrine and immunologic systems (Barja-fidalgo *et al*., 2003). Taylor *et al*. (1967) studied the effects of intrauterine malnutrition on the intensity of inflammatory response and concluded that the reticuloendothelial system is depressed, lessening the quality with which macrophages are formed in various tissues. The local inflammatory response was greatly influenced by malnourishment; there was a delay in tissue repair in rats, as the nourished animals exudate presented fibroblasts with collagen deposits – which was not found in the malnourished animals exudate. In this context, the objective of this study is to review in literature the effects of fetal programming in the inflammatory response in Wistar rats.

MATERIAL AND METHOD

In order to carry out this study were we consulted the following databases: SciELO (Scientific Electronic Library Online); MEDLINE (US National Library of Medicine); PUBMED (National Library of Medicine and The National Institute of Health); SCIENCE DIRECT; SCOPUS; LILACS (Latin American and Caribbean Health Sciences) and SPRINGERLINK. The searching strategy involved the following databases, with these respective search terms: on SciELO, “malnutrition and inflammation”; on MEDLINE, "malnutrition" [subject descriptor] and "inflammation" [subject descriptor]; and “Wistar rats” [subject descriptor]; on PUBMED, “early malnutrition and chronic inflammatory response” and “early malnutrition and inflammatory response and rats”. On SCIENCE DIRECT, “intrauterine malnutrition and inflammation and rats”; on SCOPUS, “early malnutrition AND inflammation AND rats” and “fetal programming and inflammation and rats” for a second search. On LILACS, "malnutrition" [subject descriptor] and "inflammation" [subject descriptor]. On SPRINGERLINK, “intrauterine malnutrition and inflammation and rats”.

Were included original articles involving albino rats. Were excluded review articles as well as those involving human beings and animals different from rats, as well as the articles that related malnutrition that was not intrauterine and did not involve the fetal programming concept. Those articles that were found in more than one of the explored databases were counted only once.

On the SciELO, PUBMED, LILACS and SCIENCE DIRECT databases no limits were established, whereas on the MEDLINE, SCOPUS, SCIENCE DIRECT and SPRINGERLINK databases were explored the articles published on the following periods, respectively:1966-2009; 2004-2009; 1996-2009; 1996-2009. 16 articles were found on PUBMED, 16 on SCOPUS, 4 on MEDLINE, 341 on SCIENCE DIRECT, 8 on SciELO, 1 on LILACS and 77 on SPRINGERLINK, totalizing 463 articles. From these, after applying the inclusion and exclusion criteria, 4 were selected for analysis.

The selected articles were critically analyzed through an interpretation guide, used to evaluate their individual quality, based on the studies of Greehalgh (1997) and adapted from Mcdermid *et al*. (2009). The articles quality evaluation items are expressed as scores in Table I.

RESULTS

Table II shows search results after applying the inclusion and exclusion criteria.

Table I. Quality of the studies about intrauterine malnutrition and inflammation.

Studies	Evaluation criteria items*												
	1	2	3	4	5	6	7	8	9	10	11	12	Total (%)
Landgraf *et al*. (2008)	2	2	2	2	2	1	2	1	2	1	1	1	79.1
Torrens *et al*. (2009)	2	2	2	2	2	2	2	2	1	1	1	2	87.5
Landgraf *et al*. (2007)	2	2	2	2	2	1	2	2	0	1	1	2	79.1
Landgraf *et al*. (2005)	2	2	2	2	2	1	2	2	2	1	1	1	83.3

* Evaluation criteria: 1. Bibliographic review of detailed relevant backgrounds. 2. Exclusion criteria. 3. Specific hypothesis. 4. Adequate malnourishment and inflammation scope. 5. Sample size. 6. Follow-up. 7. Referred authors, good methodological execution. 8. Measurement techniques standardization. 9. Presented data for each hypothesis. 10. Adequate statistics. 11. Adequate statistical error estimation. 12. Valid conclusions and clinical recommendations.

Table II. Studies that evaluated the effects of intrauterine malnutrition in the inflammatory response in Wistar rats.

Study	Sample characteristcs	Evaluation instruments and methods	Main results
Landgraf *et al.* (2008)	Wistar rats malnourished during gestation	Lung inflammation induction.	Low weight on birth for the malnourished litter (P<0.001). Intrauterine malnutrition reduces pulmonar allergic inflammatory response.
Torrens *et al.* (2009)	20 Wistar rats (6 nourished e 14 malnourished during gestation)	Usage of reagents: inflammation biomarkers.	Intrauterine malnutrition causes endothelial dysfunction with inflammation. Atorvastatin may delay the beginning of the endothelial dysfunction.
Landgraf *et al.* (2007)	16 male animals. 8 on the control and 8 on the experimental groups	Inflammatory response induction with TNF on the animals scrotum	Medullary hypocellularity. decrease in the LTB4 and L-selectin levels. alteration of basal membrane composition with collagen IV reduction. reduction in leukocytary migration.
Landgraf *et al.* (2005)	17 male Wistar rats. 9 malnourished during gestation and 8 nourished	Inflammation induction through Zymosan (SIGMA).	Leucopenia. reduction in ICAM-1. P-selectin and L-selectin in rats that were malnourished during gestation. Reduction of leukocytary migration.

DISCUSSION

A nutritional imbalance during the intrauterine development phase has predisposed the offsprings to diseases during adult life. Low weight at birth has been verified in these litters (Franco *et al*., 2002; Falkner, 2002; Landgraf *et al.*, 2005), When maternal diet is restricted, the nutrients availability for transplacental transport is decreased, thus reducing the nutrients supplying the fetus and limiting its growth (Holemans *et al*., 2003).

Diseases like arterial hypertension, type 2 diabetes and renal hemodynamic dysfunctions have been frequently studied (Woods *et al.*, 2001).

Limited evidence exists to explain the immune system compromising during the adult phase of offsprings that underwent intrauterine malnourishment. It has been reported that the morphogenesis (in quantitative terms) in the red bone marrow has been compromised, as well as the defense cells action mechanism (Landgraf *et al.*, 2007).

The inflammatory response is a defense mechanism beneficial for the body with unspecific reaction. In other words, any aspect such as the activation of factors like the activated beta globulin (Hageman factor), as well as the tissue lesion itself, may be a signal for the inflammatory response start. The inflammation effectiveness needs a good leukocyte margination in the direction of the vascular endothelium, a good aggregation to this endothelium and an effective directing of these leukocytes to the inflammatory site.

The leukocytary migration to the inflammatory site involves many stages that need a reduction in the local blood flow, favoring the adhesion (to the endothelium) process (Forlow *et al.*, 2000). Both increased permeability and vascular dilatation, associated with the increase in platelet adhesion and hemoconcentration corroborate for a circulatory retardation in the affected area. In these circumstances the figurative elements, which normally transit in the center of the blood flow, distribute through the liquid column and endothelium, facilitating the leukocyte adhesion to the endothelium with posterior migration to the interstitial region (diapedesis) and directing for the inflammatory site (chemotaxis). The pavementing process is related to the endothelium ionic charge and to the presence of proteins (adhesins): selectins, immunoglobulins and integrins, which may be produced by both leukocytes and endothelial cells. On the studies of Chandra & Ghai (1976) the mobilization of polymorphonuclear cells to the inflammatory site was deficient in malnourished individuals, causing a deficiency in the inflammatory process. Barja-Fidalgo et al. showed for the first time that malnutrition during the first days of lactation in Wistar rats causes permanent alterations in the programming of insulin and glucocorticoid secretion. Other works have demonstrated that alterations to the inflammatory response development occur in the insulin-deficient state (Kamata *et al*., 1992). These alterations have also limited the production of a good acute inflammatory response on adult life. These responses may be due to deficiencies in the leukocyte-endothelium interactions, mainly in the pavementing process, as the malnourished animals had lower ICAM-1 (intercellular-adhesion-molecules) expression. On the studies of Landgraf *et al.* (2005) intrauterine malnutrition caused a significant reduction in the ICAM-1, P-Selectin and L-Selectin – as

well as leucopenia – expressions on adult rats, what decreased the leukocyte migration to the inflammatory site, predisposing the malnourished offspring to infections. The ICAM-1 is an immunoglobulin that has important role in the adhesion and leukocytary pavementing processes and consequent transendothelial migration during an inflammation, regulated by different chemical mediators and cytokines that modulate its expression intensity. This reduced expression may lessen the leukocyte capability – mainly the polymorphonuclear ones – to adhere to the endothelium, reducing the inflammatory response efficiency (Bechard *et al.*, 2001). On the studies of Aljada et al. (2000) insulin decreased the ICAM-1 expression through the increase in the nitrous oxide expression. As for the L-selectin, it has an important role in regulating the leukocyte rolling speed, which can retard the migration process if its expression is reduced (Rainer, 2002).

In the studies of Landgraf *et al.* (2008) intrauterine malnutrition significantly reduced the E immunoglobulin antigen (IgE) production, as well as the production and infiltration of inflammatory cells in the airways, mucus secretion, leukotriene B4 (LTB4), along with the increase in corticosterone levels on the adult offspring. The decrease in the production of LTB4 impairs the adhesion functions, the increase in vascular permeability and chemotaxis, resulting in a reduction in the inflammatory mechanism efficiency. It is well-established that malnutrition affects the hypothalamic-pituitary-adrenal system, increasing its activities, resulting in adrenal hypertrophy, followed by corticosteroids hyperproduction. On Lesage *et al*. (2002) studies with rats these alterations affected the metabolic homeostasis, also compromising the innate defense mechanism. High glucocorticoid levels inhibit the action of various inflammatory mediators, reduce the chemokynes and cytokines and jeopardize the leukocyte activation, weakening the inflammatory process (Barja-Fidalgo *et al*.).

The inflammatory response intensity is mediated by inflammation chemical mediators, among them histamine, plasmatic systems, cytokines and arachidonic acid metabolic residues.

On the studies of Faggioni *et al*. (2001) the macrophages phagocytosis effectiveness was compromised in rats with low leptin level. This protein is mainly produced by the adipose tissue, which has pleiotropic function, regulating metabolic, endocrine and immunologic functions. Your receptors are homologous to the GP130, interleukin-6 subunit signal transduction factor. This resemblance has conducted studies to suggest that it may be classified as a cytokine. The leptin levels increased during acute inflammation, which may be a defense component of the host. On the other hand, leptin deficiency has increased the organism's susceptibility to infections and inflammations. The results of the aforementioned studies suggest that leptin may have altered the macrophages phenotypes.

CONCLUSION

Fetal programming seems to interfere with inflammatory response in the adult offspring of Wistar rats, although its mechanisms remain yet uncertain. More studies for the comprehension of these factors are suggested.

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RESUMEN: El objetivo de este trabajo fue revisar la literatura sobre los efectos de la programación fetal en la respuesta inflamatoria en ratas Wistar. Se realizó una búsqueda en las bases de datos: PubMed, MEDLINE, PUBMED, Science Direct, SCOPUS, LILACS, SpringerLink. Los términos principales de la búsqueda fueron la malnutrición y la inflamación y se buscaron en portugués e inglés. Se incluyeron artículos originales de ratas albinas y se excluyeron los artículos de revisión, las relacionadas con los seres humanos o animales, y de ratas en los artículos relacionados a la desnutrición, que no era el intrauterina y que no se referían al concepto de la programación fetal. Los artículos encontrados en más de una base de datos se contaron una sola vez. Encontramos 16 artículos en PUBMED, 16 en SCOPUS, 4 en MEDLINE, 341 en Science Direct, 8 SciELO, LILACS y 1 de cada 77 en SpringerLink, dando un total de 463 artículos. Después de la aplicación de la inclusión y exclusión de criterios fueron seleccionados 4 artículos para el análisis. La programación fetal parece interferir con la respuesta inflamatoria en los descendientes adultos de ratas Wistar, pero sus mecanismos siguen siendo inciertos.

PALABRAS CLAVE: Programación fetal; Inflamación; Ratas Wistar; Revisión sistemática.

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