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EFEITOS DO CONSUMO DE FRUTOSE DURANTE A GESTAÇÃO E LACTAÇÃO E SUA REPERCUSSÃO NA VIDA PÓS-NATAL: ESTUDO DE PROGRAMAÇÃO METABÓLICA EM RATOS MACHOS

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RESUMO

SILVA, R. J. **Efeitos do consumo de frutose durante a gestação e lactação e sua repercussão na vida pós-natal: estudo de programação metabólica em ratos machos.** 175 f. Tese (Doutorado em Ciências Morfofuncionais) - Instituto de Ciências Biomédicas, Universidade de São Paulo, São Paulo, 2017.

INTRODUÇÃO: A exposição materna à frutose durante a gestação e lactação pode contribuir para o desenvolvimento de doenças crônicas na vida adulta da prole, mediado por alterações periféricas relacionadas ao metabolismo hepático glicídico e lipídico, e na via de sinalização de insulina, podendo provocar alterações centrais relacionadas à via de sinalização da leptina e de neuropeptídios envolvidos no controle do comportamento alimentar. **OBJETIVO:** Estudar os efeitos da ingestão de frutose durante a gestação e lactação sobre a vida pós-natal no que diz respeito às alterações metabólicas, de expressão gênica e ao comportamento alimentar em ratos machos. **METODOLOGIA:** Foram utilizados ratos machos da linhagem Sprague-Dawley, sacrificados nos 14º e 90º dias de vida pós-natal completos, provenientes de mães alimentadas com ração controle (AIN-93) e de mães alimentadas com ração rica em frutose (60%), ambas isocalóricas, durante (i) a gestação; (ii) a lactação e (iii) gestação e lactação. Após o desmame, a prole foi alimentada com ração controle (AIN-93) até os 91 dias de vida. Foram analisados os seguintes parâmetros: biométricos, dietéticos e metabólicos (glicemia, concentração sérica de leptina, de insulina) e de neuropeptídios envolvidos no controle do comportamento alimentar (AgRP, CART e MCH), sensibilidade periférica à ação da insulina, expressão de proteínas envolvidas com a via de sinalização da insulina e deposição hepática de lipídios. **RESULTADOS:** Frente a dieta materna rica em frutose na gestação e na lactação, houve redução do índice de Lee no nascimento e hipoleptinemia aos 90 dias de vida (apenas nas proles que as mães consumiram frutose na gestação), intolerância à glicose na vida pós-natal desde o desmame, concomitante com alterações na sensibilidade à ação da insulina na vida adulta, hiperinsulinemia, dislipidemia (elevação da concentração de TG e de LDL-colesterol e redução da concentração de HDL-colesterol), deposição hepática de TG, estímulo hedônico do comportamento alimentar alterado aos 14 dias de vida pós-natal via núcleo *accumbens shell* com maior expressão gênica de CART. **CONCLUSÃO:** Proles provenientes de mães que consumiram ração rica em frutose durante a gestação e/ou lactação, possuem possível marca epigenética que pode contribuir para o prejuízo na produção e ação da insulina, ocasionando alterações na homeostase do metabolismo glicídico e lipídico hepáticos, levando a deposição hepática de gordura, alterações no perfil lipídico e no controle hedônico central do comportamento alimentar.

Palavras-chave: Programação metabólica. Frutose. Risco cardiometabólico. Comportamento alimentar. Genômica nutricional.

ABSTRACT

SILVA, R. J. **Effects of fructose consumption during gestation and lactation and its repercussion on postnatal life: a metabolic programming study in male rats.** 175 p. Thesis (Ph.D. in Morphofunctional Sciences) - Institute of Biomedical Sciences, University of São Paulo, São Paulo, 2017.

INTRODUCTION: Maternal exposure to fructose during gestation and lactation can contribute to the development of chronic diseases in the adult life of offspring, mediated by peripheral alterations related to glucose and lipid metabolism of the liver, and in the insulin signaling pathway, which may lead to central alterations related to the signaling pathway of leptin and neuropeptides involved in the control of eating behavior. **OBJECTIVE:** To study the effects of ingestion of fructose during gestation and lactation on postnatal life with respect to metabolic changes, gene expression and feeding behavior in male rats. **METHODS:** Male Sprague-Dawley rats were sacrificed on the 14th and 90th days of postnatal life, from mothers fed with control rat chow (AIN-93) and from mothers fed a high fructose diet (60%). Both isocaloric, during (i) gestation; (ii) lactation and (iii) gestation and lactation. After weaning, the offspring were fed with control rat chow (AIN-93) until the 91st days of life. The following parameters were analyzed: biometric, dietary, metabolic (glycemia, serum concentration of leptin, insulin) and neuropeptides involved in food behavior control (AgRP, CART and MCH), peripheral sensitivity to insulin action, expression of proteins involved with the insulin signaling pathway and hepatic deposition of lipid. **RESULTS:** A maternal diet high in fructose during gestation and lactation had a reduction in the Lee index at birth and hypoleptinemia at 90 days of age (only in the offspring that the mothers consumed fructose during pregnancy), glucose intolerance in postnatal life since with changes in insulin sensitivity in adult life, hyperinsulinemia, dyslipidemia (elevation of TG and LDL-cholesterol, reduction of HDL-cholesterol), hepatic deposition of TG, and in the central hedonic control of dietary behavior altered at 14 th days of postnatal life via the nucleus accumbens shell with greater gene expression of CART. **CONCLUSION:** The offspring from mothers who consumed fructose rat chow during gestation and / or lactation have a possible epigenetic mark that may contribute to the impairment in the production and action of insulin, leading to alterations in hepatic glucose and lipid metabolism homeostasis, leading to hepatic fat deposition and alterations in the lipid profile, and in the central hedonic control of dietary behavior.

Keywords: Metabolic programming. Fructose. Cardiometabolic risk. Food behavior. Nutritional genomics.

1 INTRODUÇÃO

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A ocidentalização da alimentação é um dos fatores da transição nutricional que ocorre em todo o mundo, com aumento da disponibilidade de alimentos de elevado teor calórico e ricos em frutose, como refrigerantes e alimentos pré-preparados (processados e ultraprocessados), que contribuem para o aumento da prevalência de síndrome metabólica (SM) (SILVA et al*.,* 2011; MINISTÉRIO DA SAÚDE, 2014).

Evidências demonstram que doenças crônicas não transmissíveis (DCNT), como diabetes melito tipo 2 (DM 2), hipertensão arterial sistêmica (HAS), aterosclerose e doenças cardiovasculares (DCV), podem ter origem em alterações ocorridas no útero e/ou durante o início da vida pós-natal (JOSHI et al*.,* 2003).

A maioria dos estudos sobre programação metabólica é realizada com modelos animais que induzem subnutrição materna, ou por meio do consumo de ração hiperlipídica pelas mães, o que aumenta o risco de obesidade, resistência à ação da insulina (RI) e diminuição da sensibilidade à leptina pela prole, independentemente do tipo de ração ingerida pós-parto (HOWIE et al*.,* 2009; VICKERS, 2011a). No entanto, há escassez de estudos utilizando a frutose e seu impacto na programação metabólica. Neste contexto, os efeitos da ingestão materna de frutose sobre a saúde da prole ainda são pouco conhecidos, apesar do recente aumento do consumo de bebidas e alimentos com alto teor de frutose (ALZAMENDI et al., 2016; VICKERS, 2011a).

Tendo em vista que a SM é uma condição clínica que vem tomando proporções epidêmicas nos últimos anos, mostra-se de suma importância o estudo das consequências do consumo de frutose desde a sua exposição precoce.

Frente ao exposto, este trabalho busca entender melhor os mecanismos envolvidos no desenvolvimento da SM, ocasionado pelo consumo materno de frutose, uma vez que, a prole pode sofrer alterações irreversíveis tanto metabólicas, como no e no comportamento alimentar, podendo culminar no desenvolvimento de DCNT na vida adulta.

1.1 Justificativa

Tendo em vista que a SM é uma doença que vem tomando proporções epidêmicas nos últimos anos, mostra-se de suma importância o estudo das consequências do consumo de frutose desde a sua exposição no período perinatal.

A maior parte dos nossos conhecimentos sobre a ação de nutrientes e compostos bioativos dos alimentos sobre a programação metabólica é oriundo de estudos com restrição alimentar, restrição proteica, ou dietas ricas em lipídios totais ou saturados.

Dessa forma, na busca de um modelo experimental adequado ao estudo da SM/RCM, o presente trabalho foi delineado para analisar a tolerância à glicose, a sensibilidade à insulina, perfil lipídico e alterações neuroendócrinas em ratos descendentes de mães mantidas com ração rica em frutose nos períodos gestacional e lactacional, uma vez que, a frutose tem sido um nutriente associado ao desenvolvimento dos fatores de risco associado.

1.2 Hipótese

A exposição materna à frutose durante a gestação e lactação contribui para o desenvolvimento de DCNT na vida adulta da prole, mediado por alterações periféricas relacionadas ao metabolismo hepático glicídico e lipídico e na via de sinalização de insulina, bem como por meio de alterações centrais relacionadas a via de sinalização de leptina e de neuropeptídios envolvidos no controle do comportamento alimentar.

7 CONCLUSÃO

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Frente aos objetivos propostos e aos resultados obtidos, podemos concluir que a ingestão de frutose pelas mães durante os períodos críticos de desenvolvimento fetal e infantil favorece na descendência:

- ✓ Redução do índice de Lee (peso/comprimento) no nascimento apenas nas proles que as mães consumiram frutose na gestação;
- ✓ Intolerância à glicose na vida pós-natal desde o desmame, concomitante com alterações na sensibilidade à ação da insulina na vida adulta;
- ✓ Hiperinsulinemia;
- ✓ Hipoleptinemia apenas nas proles que as mães consumiram frutose na gestação;
- ✓ Dislipidemia (elevação de TG e LDL-colesterol, com redução do HDL-colesterol);
- ✓ Comprometimento hepático com deposição hepática de TG;
- ✓ Controle hedônico do comportamento alimentar alterado aos 14 dias de vida via núcleo AcbSh.

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