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FACULDADE DE MEDICINA

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Estudo do efeito do N-acetil-cisteína através do metabolismo energético, complexos respiratórios e estresse oxidativo no tecido hepático de ratos submetidos ao glutamato monossódico

Tese apresentada à Faculdade de Medicina, Universidade Estadual Paulista "Júlio de Mesquita Filho", Câmpus de Botucatu, para obtenção do título de Doutor em Fisiopatologia em Clínica Médica.

Orientadora: Profª. Drª. Ana Angélica Henrique Fernandes

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1. Estresse oxidativo. 2. Metabolismo energético. 3. Figado - Doenças. 4. Calorimetria. 5. Aminoácidos.

Palavras-chave: Calorimetria; Estresse Oxidativo; Figado; Metabolismo energético; N-acetil-cisteína.

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RESUMO

A obesidade é considerada um dos maiores problemas de saúde pública em muitos países, uma vez que está associada queda da qualidade de vida. Embora existam vários fatores que corroboram com o desenvolvimento para tal fato, os hábitos alimentares seja o fator relevante. Os transtornos metabólicos podem resultar em alterações na funcionalidade do fígado, podendo desenvolver Doença Hepática Gordurosa Não Alcoólica (DHGNA). Como o número de obesos e as co-morbidades associadas ao sobrepeso vêm aumentando abruptamente nas últimas décadas, vários modelos de obesidade experimental têm sido propostos para investigar os distúrbios metabólicos envolvendo suas causas e consequências. O glutamato monossódico é amplamente utilizado na culinária e também por indústrias alimentícias, contudo atua no sistema nervoso central e promove a degeneração de áreas importantes do hipotálamo que leva a distúrbios da saciedade e, consequentemente acúmulo excessivo de gordura abdominal. Com a finalidade de estudar substâncias que apresentem potencial atividade terapêutica no controle dos distúrbios metabólicos, o N-acetil-cisteína possui propriedades antioxidantes e exerce hepatoproteção. Desta forma, o objetivo do presente estudo foi evidenciar a indução da obesidade pelo glutamato monossódico e determinar o efeito do N-acetil-cisteína sobre os parâmetros calorimétricos, metabolismo energético, atividade dos complexos respiratórios e estresse oxidativo no tecido hepático. Foram utilizados 32 ratos Winstar, machos com 21 dias de idade. Inicialmente os animais foram distribuídos em dois grupos experimentais (*n*=16). O grupo C foi o controle e receberam dieta padrão; o grupo GMS recebeu dieta padrão contendo glutamato monossódico (GMS),

durante 30 dias. Após este período estes grupos (C e GMS) foram subdivididos (*n*=8) em NAC que recebeu o mesmo tratamento de do grupo C e a administração de N-acetil-cisteína e o grupo GMS-NAC que recebeu o mesmo tratamento do grupo GMS e a administração de N-acetil-cisteína.Estes grupos foram mantidos durante 30 dias. Os animais receberam N-acetil-cisteina na concentração $30mg^{-1}$dia através da via intra-gástrica (gavage). O delineamento estatístico foi inteiramente ao acaso com 32 tratamentos e 8 repetições, com nível de significância de 5% de probabilidade. O peso corporal diminuiu ($p<0.05$) em animais do grupo GMS-NAC em relação aqueles do grupo NAC, o qual não deferiu dos grupos C e GMS. A calorimetria revelou menor oxidação de carboidratos e maior oxidação de lipídios com elevada atividade da β-hidroxacil-CoA-desidrogenase em GMS. Estes animais também apresentaram menor HDL-colesterol sérico e acúmulo anormal de triacilgliceróis, além de promover o estresse oxidativo no tecido hepático. A administração de N-acetil-cisteína ameizou as alterações metabólicas (aumentou oxidação de carboidratos e diminuiu a oxidação de lipídios), manteve a homeostase da glicose, aumentou a concentração de HDL-colesterol e atenuou o estresse oxidativo. Desta forma, pode-se concluir que a dose administrada de N-acetil-cisteína atenuou os efeitos deletérios impostos pelo comportamento alimentar inadequado, normalizou o metabolismo energético, manteve a homeostase da glicose e reduziu o acúmulo de triacilgliceróis no tecido hepático.

Palavras Chave: Disfunção metabólica; Glutamato monossódico; N-acetil cisteína; Metabolismo Energético; Estresse Oxidativo;

ABSTRACT

Obesity is considered one of the greatest public health problems in many countries, since it is associated with a drop in quality of life. Although there are several factors corroborating with the development for this fact, eating habits are the relevant factor. Metabolic disorders can result in changes in liver function, and can develop Non-Alcoholic Fatty Liver Disease (NAFLD). As the number of obese and co-morbidities associated with overweight have increased steeply in recent decades, several models of experimental obesity have been proposed to investigate metabolic disorders involving their causes and consequences. Monosodium glutamate is widely used in cooking and also in food industries, but it acts on the central nervous system and promotes the degeneration of important areas of the hypothalamus which leads to satiety disorders and consequently excessive accumulation of abdominal fat. In order to study substances that present potential therapeutic activity in the control of metabolic disorders, N-acetyl-cysteine has antioxidant properties and exerts hepatoprotection. Thus, the objective of the present study was to evidence the induction of obesity by monosodium glutamate and to determine the effect of N-acetyl-cysteine on calorimetric parameters, energy metabolism, respiratory complex activity and oxidative stress in hepatic tissue. Thirty-two Winstar male mice were used at 21 days of age. Initially the animals were distributed in two experimental groups (n = 16). Group C was the control and received standard diet; the GMS group received standard diet containing monosodium glutamate (GMS) for 30 days. After this period these groups (C and MSG) were subdivided (n = 8) into NAC who received the same treatment as group C and administration of N-acetyl cysteine and the GMS-NAC group that received the

same treatment as the group GMS and administration of N-acetyl-cysteine. These groups were maintained for 30 days. The animals received N-acetyl-cysteineat the 30mg^{-1}day concentration through the intragastric route (gavage). The statistical design was completely randomized with 32 treatments and 8 replicates, with a significance level of 5% of probability. Body weight decreased ($p<0.05$) in animals in the GMS-NAC group compared to those in the NAC group, which did not differ from the C and GMS groups. Calorimetry revealed lower carbohydrate oxidation and higher lipid oxidation with high β-hydroxacil-CoA dehydrogenase activity in GMS. These animals also presented lower serum HDL-cholesterol and abnormal accumulation of triacylglycerols, in addition to promoting oxidative stress in liver tissue. N-acetyl-cysteine administration ameliorated metabolic changes (increased carbohydrate oxidation and decreased lipid oxidation), maintained glucose homeostasis, increased HDL-cholesterol concentration and attenuated oxidative stress. Thus, it can be concluded that the administered dose of N-acetyl-cysteine attenuated the deleterious effects imposed by the inadequate alimentary behavior, normalized the energy metabolism, maintained glucose homeostasis and reduced the accumulation of triacylglycerols in the hepatic tissue.

Key Words: Disfunction metabolic; Glutamate monosodium; N-acetyl-cysteine; Energetic metabolism; Oxidative Stress.

SUMÁRIO

CONCLUSÃO

Diante dos resultados obtidos conclui-se que a dieta acrescida de glutamato monossódico induziu alterações metabólicas, com diminuição na oxidação de carboidrato em detrimento à oxidação excessiva de lipídios. Além disso, promoveu o acúmulo de triacilgliceróis e estresse oxidativo, no tecido hepático. A dose administrada de N-acetil-cisteína atenuou os efeitos deletérios impostos pelo comportamento alimentar inadequado, normalizou o metabolismo energético, manteve a homeostase da glicose e reduziu o acúmulo de triacilgliceróis no tecido hepático. Os efeitos benéficos observados pela administração de N-acetil-cisteína estiveram associados à ação protetora das defesas antioxidantes contra o estresse oxidativo no fígado.

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