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Review Article

Macronutrients and the FTO gene expression in hypothalamus; a systematic review of experimental studies

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ABSTRACT

The various studies have examined the relationship between FTO gene expression and macronutrients levels. In order to obtain better viewpoint from this interactions, all of existing studies were reviewed systematically. All published papers have been obtained and reviewed using standard and sensitive keywords from databases such as CINAHL, Embase, PubMed, PsycInfo, and the Cochrane, from 1990 to 2016. The results indicated that all of 6 studies that met the inclusion criteria (from a total of 428 published article) found FTO gene expression changes at short-term follow-ups. Four of six studies found an increased FTO gene expression after calorie restriction, while two of them indicated decreased FTO gene expression. The effect of protein, carbohydrate and fat were separately assessed and suggested by all of six studies. In Conclusion, The level of FTO gene expression in hypothalamus is related to macronutrients levels. Future research should evaluate the long-term impact of dietary interventions.

Contents

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1. Introduction

Obesity is a major public health challenge worldwide in 21 century.[1] Obesity has important role in a large number of diseases, including coronary heart disease, type 2 diabetes, cancer, hypertension, dyslipidemia and stroke.[2–5] The prevalence rates of overweight and Obesity are worriedly increasing in the worldwide. More than 12% of the adult population are obese.[6] Obese adolescents were reached from 5% to 21% from 1980 to 2012.[7]

The role of various factors in the formation and progression of obesity has been shown. Genetics, life style and environmental factors are the most important factors that have been associated with obesity.[8] Numerous studies have reported that unhealthy lifestyle including low physical activity and poor nutrition are the main cause of obesity[9–13] and, therefore, suggested lifestyle changes as strategies to prevent and combat obesity.[14–19] On the other hand it has also been noticed that even with lifestyle changes, the success rate in reducing obesity is not always satisfactory.[20] Here the role of genetics in obesity is highlighted as an explanation to this dilemma. The results of recent studies in the field of nutritional genomics create uncertainties in understanding the role and importance of lifestyle in occurring obesity and/or decrease imagined role of the lifestyle in obesity.

Several studies have explored the interactions between genomics and diet and its relationship with hyperlipidemia and hypertension.[21–25] Recent studies in the field of nutritional genomics have demonstrated that genetic background plays an important role not only in probability of occurring obesity but also in people's response to the lifestyle intervention.[26–34] Several genes have been studied in relation to obesity, which one of the most important genes is FTO (Fat mass and obesity-associated protein).

FTO gene expression is associated with regulation of food intake and energy balance.[35–41] Also recent studies have tried to explore the interaction of dietary components with FTO gene expression in hypothalamus. As there is no systematic review on these studies, this study aims to fill this gap and contribute to better understanding of the interaction of dietary components and FTO gene expression.

2. Methodology

2.1. Data sources

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines that have been used for other gene expression-related systematic reviews.[42] The search covered all available research from January 1990 to January 2016 in CINAHL, Embase, PubMed, PsycINFO, and the Cochrane Library. The bibliographies of included articles were hand-searched, and promising titles were reviewed in order to locate articles not catalogued in the major databases. In cases that reviewer was unable to determine whether an article pertained to the study by title, the abstract was reviewed. The search terms used were (Body Mass Index OR Body Weight OR Obesity OR Overweight OR obese OR FTO gene OR FTO gene expression OR hypothalamus OR diet OR dietary component OR calorie OR calorie restriction OR protein OR carbohydrate OR fat OR macronutrient.

This systematic review compares randomized controlled trials studies that utilized dietary interventions including dietary macronutrients modifications as interventions to change the level of FTO gene expression. This review involves assessing dietary interventions delivered through changes in macronutrients levels to influence on FTO gene expression. Inclusion criteria consisted of: randomized trials or trials without randomization or a control group; a primary outcome including FTO gene expression; trials that tested dietary interventions (through diet modification) and subjects included rats and mice. Papers were excluded if the articles were published in a language other than English.

2.2. Data extraction

The studies focused primarily on changes in calorie,[36–39] fat,[37,40] amino acid (Leucine),[36,41] and carbohydrate (Sucrose) intake or administration.[37,39]

2.3. Outcome variables

The initial search generated a total of 428 papers from all the search databases. To obtain rigorous scientific evidence, only randomized controlled trials studies were selected for this systematic review in terms of key outcomes and interventions used. One reviewer screened the study title and abstract as the first screening stage and narrowed the articles to 334 papers. Two reviewers then reviewed the abstract and narrowed the search from 334 articles to 85 articles by eliminating duplicate papers based on the same research. Articles that were nonintervention studies, such as review papers, and cross-sectional studies were also excluded. The primary outcome was change of FTO gene expression with the use of macronutrients. Studies that did not target FTO gene expression and were not macronutrients-based

Table 1
Methodological rigor of included studies.

Reference	Randomization	Blinding	Inclusion/exclusion criteria clearly described	Adequate sample sizecalculationsshown	Adequate control group*	Standard measures described	Comparison of baseline parameters of completers versusnoncompleters	80% retention rate**	MR score
Gutierrez-Aguilar et al.[41]	0	0	1	1	1	1	1	1	6
Olszewski et al.[37]	0	0	1	1	1	1	1	1	6
Boender et al.[38]	0	0	1	1	1	1	1	1	6
Johansson et al.[42]	1	0	1	1	1	1	1	1	7
Fredriksson et al.[39]	1	0	1	1	1	1	1	1	7
Poritsano et al.[40]	1	0	1	1	1	1	1	1	7

Notes: *Control group was reflective of study group in number, age and sex; **80% of participants completed the intervention.
Abbreviations: MR: methodological rigor.

were excluded. Based on the inclusion criteria, two reviewers examined the full papers and identified 6 studies that met the inclusion criteria (see Table 1).

2.4. Intervention components

Detailed examination of the following components of effective interventions was conducted: macronutrient intake or administration, method used for intake/administration changes, subjects, and duration of the intervention. The effectiveness of the intervention was determined by reviewing the results of the study and reporting the study findings.

2.5. Assessment of methodological rigor

Methodological rigor assessment was adapted to include articles from those in use by the Cochrane Effective Practice and Organization of Care Review Group and recent systematic reviews.[42] The eight criteria were scored objectively using published data and reflect potential bias (see Table 1). Studies were rated independently by two reviewers. Each item was rated as "yes" (1), "no" (0), or "not applicable". A total methodological quality score (ranging from 0 to 8) was calculated by summing up all "yes" items. Studies were rated as having good methodological quality if they met at least 75% of the criteria (six of eight items).

3. Results

3.1. Components of effective interventions

Two protein-based interventions, two fat-based interventions and two carbohydrate-based interventions were included in this systematic review. All of 6 studies indicated the effectiveness of macronutrients on FTO gene expression.

3.2. Effect of calorie restriction

Four of six studies found that macronutrients intake decreased FTO gene expression (36, 37, 38 and 40) and two study reported that 48-h food deprivation had reduced FTO gene expression (39 and 41).

3.3. Effect of increased dietary fat

Two of the six studies that examined the impact of increased dietary fat found reduced FTO gene expression after intervention.[38,41] For instance, a study by Gutierrez-Aguilar et al.[40] on tailored high fat diet interventions for Wistar male rats found a significant decrease in FTO gene expression at 6 weeks post intervention. Although, Boender et al. reported a non-significant reduction of FTO expression after 8-day high-fat diet.[37]

3.4. Effect of amino acids

Two studies assessed the impact of amino acid (ie, Leucine) on gene expression outcome.[36,41] Olszewski et al. found that anorexigenic Leucine had reduced FTO gene expression in organotypic cultures of the hypothalamus at 48 h post intervention.[36] While Johansson et al. found that Leucine intake had increased FTO gene expression at 48 h post intervention.[41]

3.5. Effect of carbohydrates

Two studies assessed the impact of carbohydrate administration on gene expression outcome. Poritsano et al.[39] found that increased glucose administration had increased FTO gene expression at 48 h post intervention. While Boender et al.[37] reported that increased sucrose intake had insignificantly reduced FTO gene expression at 8 days post intervention. Also, Olszewski et al. found

Table 2
Summary of Study description.

Reference	Study design	Sample characteristic	Intervention/control/components	Intervention duration	Results
Dietary fat					
Gutierrez-Aguilar et al.[40]	Experimental	30 rats (15 animals per group)	Group 1) High fat diet Group 2) normal diet	6 weeks	FTO gene expression was reduced in the high fat group
Boender et al.[37]	Experimental	24 rats (12 rats per group)	Group 1) High fat and high sucrose diet Group 2) restricted feeding Group 3) Normal diet	8 days	FTO gene expression was increased in restricted feeding group
Amino acids					
Olszewski et al.[36]	Experimental	14 mice (7 animals per group)	Group 3) 48-h supplemented with leucine Group 4) Control	48-h	−FTO gene expression was reduced in Leucine added group
Johansson et al.[41]	Experimental	16 mice (8 mice per group)	Group 1) leucine-spiked water Group 2) Water alone	48-h	FTO gene expression was increased in the intervention group
Calorie restriction					
Olszewski et al.36	Experimental	16 mice (8 animals per group)	Group 1) High calorie diet Group 2) 16-h fasting	16-h	FTO gene expression was increased in 48-h fasting group
Fredriksson et al.[38]	Experimental	24 rats (eight animals per group)	Group 1) Low calorie diet Group 2) Food-deprived Group 2) Normal diet	48-h	Expression of the FTO gene is up-regulated during starvation
Glucose					
Poritsano et al.[39]	Experimental	6–10 mice per group	Group 1) Low calorie diet And Glucose administration Group 2) Normal diet Group 3) Low calorie diet	48-h	FTO gene expression was reduced after low calorie diet and increased after Glucose administration in the intervention group

no changes in hypothalamic FTO expression after a 48-h palatable sucrose feeding (Table 2).[36]

4. Discussion

The present systematic review investigates the potential impact of dietary components (such as protein, carbohydrate and fat) on FTO gene expression. Based on this review of 6 intervention studies, there is some evidence that suggest the possibility that macronutrients affect hypothalamic FTO expression. Also most of studies (4 of 6 studies) indicated that higher macronutrients levels can decrease FTO gene expression (36, 37, 38 and 40) and two studies reported decrease FTO gene (39 and 41).

There is no clear evidence about the reason of existing contradiction between short-term and long-term effects of macronutrients on FTO gene expression. But it may depends on the wide range of FTO gene roles in hypothalamus.[43–50] The recent studies reported that FTO has a role in macronutrients metabolism.[43–45] For instance, a study by Gulati et al.[45] found an important role of FTO in matching cellular amino acids levels with mammalian target of rapamycin complex 1 (mTORC1) signaling. On the other hand, many studies found that FTO gene polymorphisms had a critical role in FTO gene expression level and its effects on obesity.[46,47] Although other studies reported that FTO gene polymorphisms weren't linked with FTO gene expression.[48,49] The literature currently available is also insufficient to examine the impact of wide range of polymorphisms on FTO gene expression.

This review suggests that both the level of calorie and the level of each macronutrients have a potential to change FTO gene expression level. Because of the variation in duration of intervention (48-h to 6 weeks), it is not clear what length of intervention is most effective. Only one study included long-term follow-up data (more than 48-h intervention),[40] and there is no enough evidence on the optimal FTO gene expression with regard to healthy weight management.

The present review emphasize on the possibility that changes in macronutrients levels affect hypothalamic FTO expression and thereby affect regulation of appetite and body weight. We need further investigation of the relationship between macronutrients and hypothalamic FTO expression in future research.

These type of studies may contribute to determining ways in which nutrition specialists and researchers can make more informed decisions about which types of macronutrients and diet are most suitable in achieving sustainable weight reduction via impact the level of FTO gene expression. Although it was not found any clear evidence of an exact effect of dietary interventions on FTO gene expression, the use of dietary modifications have the potential to assist researchers in dealing with the obesity epidemic. Future research should include mediating factors associated with the impact of dietary intervention on FTO gene expression, and should also include more long-term follow-up. In addition, assessment of FTO gene expression related health outcomes, such as obesity and Diabetes should be included in future research.

Disclosure

The authors report no conflicts of interest in this work.

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