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Original Article

Correlation of liver X receptor and abnormal metabolism in school-age children with obesity

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Abstract: Objective: To explore the sleeping condition of children and correlated factors among students at primary school, and the expression of liver X receptor (LXR), cholesterol ester transfer protein (CETP) and cyclooxygenase-2 (COX-2), and the relative factors of liver X receptor (LXR) and lipid metabolism in school-age children with obesity. Methods: A questionnaire survey was conducted among the parents of 3283 students at primary school from June 2011 to October 2011, stratified random sampling selected in four urban districts of the city. A total of 80 obese children and 51 normal controls (age and sex matched children with normal BMI) were chosen. Fasting blood were used to detect the expression levels of metabolic indexes, to declutch and culture macrophage, from which RNA was extracted. The metabolic indexes including aspartate transaminase (AST), alanine aminotransferase (ALT), glutamyl transpeptidase (GGT), total cholesterol (CHOL), triacylglycerol (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), and expression of LXR, CETP and COX-2 were detected in fasting blood. Results: the prevalence of sleeping disorders was 16.24% in the students of primary school with 18.22% in boys and 14.07% in girls. The main risk factors that affected the sleeping conditions were weight, irregular sleep, not enough sleeping time, adenoids, watching nervous TV and acute exercise before 30 min to sleep, the bedroom with TV, sleeping with their parent, anxiety of the father, the parents' bad marriage, etc. The expression levels of LXR, CETP and COX-2 in obese children were significant higher than that in control children. COX-2 and CETP were positively correlated with LXR respectively. There was no statistic difference between boys group and girls group in the expression levels of LXR, CETP and COX-2. Compared to controls, the levels of AST, ALT, GGT, CHOL, TG and LDL-C were higher while the level of HDL-C was lower in obese children. The correlation analysis found that AST, ALT, CHOL, LDL-C and BMI were positively correlated with LXR ($r=0.18\sim0.26$, $P<0.05$). Logistic regression analysis showed that AST≥40 IU/L (OR=1.076), ALT≥40 IU/L (OR=1.036), CHOL≥5.20 mmol/L (OR=2.038), LDL-C≥3.36 mmol/L (OR=2.176) and BMI≥18.9 kg/m^2 (OR=1.131) were risk factors for LXR>1. Conclusion: The main influence factors of the sleeping are the family and social environment, schoolwork burden, habits of children and their parents' high education and anxiety. Obesity on school-age children can upregulate the expression of liver X receptor and cause liver damage and abnormal lipids metabolism.

Keywords: School-age children, sleeping, obesity, liver X receptor, metabolic disorder

Introduction

With the rapid social and economic development and lifestyle changes, obesity has become a global public health problem impacted on human health. Obesity has been defined as a global epidemic by the World Health Organization [1-3]. The occurrence of obesity in children and adolescents is growing rapidly [4]. According to statistics of children with obesity from 6 to 12 years old, there is an increase of 54%, compared to that in the past 15 to 20 years [5]. Good sleep is an important guarantee for the healthy growth of children [6-8]. Many studies have found that sleep disorders are important risk factors. The poor quality of sleep is one of the most important factors that cause obesity in children. More importantly, obesity and sleep disorders can form a vicious circle. Long-term sleep disorders lead to recurrent episodes of hypoxemia and hypercapnia, resulting in a series of neurohumoral change, severe cases of obstructive sleep apnea syndrome (OSAHS) [9, 10].

In recent years, studies have shown that macrophages are the main effector cells of the innate immune response and play an important role in the metabolism of lipids and cholesterol efflux. Liver X receptor (LXR) is present in the macrophage [11, 12]. On the one hand, LXR is involved in the regulation of lipid metabolism. On the other hand, LXR can negatively regulate the expression of inflammatory genes in macrophages. LXR is a member of the nuclear receptor superfamily transcription factor, which is divided into LXRα and LXRβ, and belongs to the first subfamily of thyroid hormone receptors [13, 14]. LXR hormone is oxidized cholesterol, which is the sensor of cholesterol metabolism, and plays an important role in the regulation of adipogenesis, glucose metabolism, immune and inflammatory reactions. Obesity caused by excessive body fat can lead to abnormal aggregation of blood lipids, and can increase the risk of cardiovascular disease [15, 16].

Cyclooxygenase (COX) also known as prostaglandin G/H synthase, is the rate limiting enzyme of endogenous prostaglandins, which catalyzes the production of prostaglandins involving in a variety of physiological and pathological processes [17]. It is generally believed that there are two types of COX: COX1 and COX2. COX2 has both cyclooxygenase and myeloperoxidase activities, can induce free radical synthesis. Free radicals can make membrane lipid peroxidation increasing permeability, and attack membrane protein, intracellular enzyme, and nucleic acid prolonging the cell cycle and inducing the cell apoptosis [18, 19]. The active oxygen species (ROS) was significantly increased under high glucose condition, which enhanced the activity of COX2 promoter by activation of NF2 kappa B, leading to an increase in COX2 expression.

OSAHS patients are involved in ester metabolism and inflammation. Macrophages also play a key role in ester metabolism and inflammatory response. Inflammation is also associated with cardiovascular diseases [20]. Liver X receptor in the macrophages plays a pivotal role in the regulation of ester metabolism and inflammatory [11]. In the process of metabolic disorders and inflammatory reactions in OSAHS patients, whether there is a corresponding change in the expression of Liver X receptor and its expression in macrophage are not clear.

The aim of this study was to investigate the relationship between sleep status and obesity prevalence in pupils in Lanzhou, to analyze the risk factors related to sleep disorders in children including the environmental, family and genetic factors, to explore the expression of inflammatory mediator COX2, and LXR and its regulatory gene-cholesterol ester transfer protein (CETP) in obese children with sleep disorders, and to explore the mechanism of obesity in children with sleep disorders and its correlations within disorder of lipid metabolism and inflammation. This study provides scientific basis for prevention and treatment of sleep disorders in obese children.

Materials and methods

Objects

Stratified cluster random sampling method was used to randomly select the children in 2 primary schools and 8 primary schools in 4 districts including Chengguan, Qilihe, Anning and Xigu, in Lanzhou. In each grade of 1-6 grades in every primary school, a class of normal children was randomly selected. A total of 3283 children without infectious diseases, acute infectious diseases, other organic diseases and psychiatric diseases in the past 1 month, were included and conducted the sleep status questionnaire. In reference to the International Classification of Sleep Disorders (ICSD) combined with the characteristics of the region, the questionnaire included three parts: the general situation of the individual and the sleep status of pupils, the parents' sleep status, and the family social environment. By trained professionals to conduct a questionnaire survey, sample survey pre-survey, repeated amendments to the questionnaire. This study was approved by the Ethics Committee of the First Hospital of Lanzhou University, and the guardians of the selected subjects signed the informed consent form.

Diagnostic criteria for sleep disorders

Sleep disturbed, the average time required to fall asleep more than 30 min or wake up frequently in every night. Sleep disorder: daytime sleep, awake at night; fall asleep prematurely, or even sleep in the evening. Alien sleep: apnea, mouth breathing, snoring, bruxism, restless sleep, sleepwalking, night terrors, limb tics dur-

ing sleep, enuresis. The above situation occurs at least 2 times a week, duration of at least 1 month. The child who has more than one of the above conditions is diagnosed as sleep disorders.

Criteria for inclusion of obese children

Obese children: meet the diagnostic criteria for obesity and age 7~14 years old. Criteria for inclusion of normal control children: normal body mass index (BMI) and age 7~14 years old. Exclusion criteria: congenital hereditary metabolic diseases and neuroendocrine diseases caused secondary pathologic obesity; the recent infectious diseases; children or guardians do not consent to participate in trials or unwilling to cooperate.

Measurement of physical index

Height was measured by the vertical height gauge with the accuracy of 0.1 cm. Weight of children with light clothing was measured by the children's electronic scales with the accuracy of 0.1 kg. BMI= body mass (kg)/height (m). The physical measurement was carried out in the Department of pediatric health care in First Hospital of Lanzhou University and was measured by two physicians who had more than 3 years working experience in the assessment of physical development of children's health.

Metabolic index laboratory testing

All subjects had a low-fat diet one day prior to blood sampling. The blood samples were centrifuged to extract serum samples and were analyzed by automatic biochemical analyzer (BECKMAN-COULTER LX-20, USA). The test items included aspartate transaminase (AST), alanine aminotransferase (ALT), glutamyl transpeptidase (GGT), total cholesterol (CHOL), triacylglycerol (TG), high density lipoprotein cholesterol (HDL-C), and low density lipoprotein cholesterol (LDL-C). The metabolic indexes were detected by the professional doctors in Department of Clinical Laboratory of the First Hospital of Lanzhou University. If ALT≥40 IU/L, GGT≥50 IU/L, CHOL≥5.20 mmol/L, TG≥1.10 mmol/L, HDL-C (≥1.0 IU/L)≤1 mmol/L, or LDL-C≥3.36 mmol/L, it was diagnosed as abnormal lipid metabolism.

Detection of LXR, COX-2, and CETP

In the early morning, fasting cubital vein blood 5 ml was extracted in heparin sodium anticoagulation tube. After centrifugation, the mononuclear cells were induced to macrophages by using the phorbol 13- acetate (PMA, Shanghai bioengineering, China) according to the manufacture's instruction. Total RNA was extracted by suing TRIzol (Tarkara, China) according to the instruction, and calculated the OD260/OD280 by UV spectrophotometer. All the ratios of OD260/OD280 were 1.8~2.2. RNA was revere transcribed into cDNA. The primers used for LXR are: upstream 5'-TGTTTCTCCGTGTCCTCT-GTGT-3', downstream 5'-CACCCAACCCTTTGA-CTCTCTT-3'; the product size is 148 bp. For COX-2: upstream 5'-TCAGACGCTCAGGAAATAG-AAAC-3', downstream 5'-GGGGAAGTATGTAGG-AGTTGAAGA-3'; the product size is 208 bp. For CETP: upstream 5'-ATGCCCCTGACTGCTACCT-3', downstream 5'-CCCAATGTCTCCATCTGAAAG-3', the product size is 221 bp. For β-actin: upstream 5'-TGGCACCCAGCACAATGAA-3', downstream, 5'-CTAAGTCATAGTCCGCCTAGAAGCA-3'; the product size is 298 bp. The conditions of quantitative PCR reaction were 95°C, 30 s, 95°C, 5 s, 60°C, 20 s, 72°C, 30 s, 40 cycles. The expression of the target gene was detected by $2^{-\Delta\Delta Ct}$ method [20]. LXR>1 means that the expression of LXR is higher than that of normal control group, LXR≤1 means that the expression level of target gene LXR is lower than that of normal control group.

Statistical analysis

Data was analyzed by SPSS16.0 statistical software. Measurement data was present as mean ± standard deviation. Two groups were compared using independent samples *t* test or rank sum test. The count data was expressed as a percentage or rate using χ^2 test. The correlation of LXR and metabolic indexes was analyzed by Pearson correlation analysis. The risk factor for LXR was analyzed by Logistic regression analysis. $P<0.05$ as the difference has statistical significance.

Results

The occurrence of sleep disorders

There were 533 people who had sleep disorders in all the primary school students. There were significant differences between boys and girls. The incidence of snoring and restlessness was higher in boys than in girls. There was no significant difference between the two groups in the incidence of other factors. The most com-

Table 1. The prevalence of sleeping disorders

	N	Boy	Girl	x^2	P
Sleeping disorders	533	312	221	10.41	0.001
Sweating	197	120	77	0.728	0.394
Restless sleep	146	98	48	6.108	0.013
Bruxism	129	63	66	0.088	0.767
Speake in sleep	74	33	41	0.981	0.322
Enuresis	71	44	27	4.593	0.032
Mouth breathing	69	42	27	3.667	0.056
Snoring	62	46	16	7.086	0.008
Limb tics during sleep	42	18	24	5.099	0.024
Nocturnal awaking	16	8	8	0.495	0.482
Fall asleep prematurely	8	5	3	0.053	0.819
Easy to awake	8	4	4	1.810	0.621
Laryngeal	7	5	2	0.486	0.486
Sleepwalking	7	5	2	1.300	0.254
Wake up in the night	7	1	6	5.723	0.017
Scream, cry	6	1	5	4.383	0.036
Apnea	3	1	2	0.790	0.374

mon incidence of sleep disorders in the top were sweating, restless sleep, bruxism, speaker in sleep, enuresis, mouth breathing, snoring, and limb tics during sleep (**Table 1**).

Risk factors for sleep disorders

The incidence of sleep disorder set as the dependent variable, the variables possibly related to children's sleep disorders as independent variables. By logistic regression analysis, there are 10 variables eventually into the regression equation of children's sleep disorders, such as weight, irregular sleep, not enough sleeping time, sleeping with their parent, the time of going to bed of fosterer, adenoids, watching nervous TV before 30 min to sleep, acute exercise before 30 min to sleep, the bedroom with TV, anxiety of the father, and the parents' bad marriage (**Table 2**).

General information of obese children

In this study, 131 cases were included in the study. A total of 80 cases obese children were included, male 65 cases and female 15 cases. The average BMI is 23.60±3.71 (19.0~39.27); average age is 9.45±1.78 years old (7.0~13.0 years). A total of 51 cases normal control children were included, male 42 cases, female 9 cases. The mean BMI is 16.63±2.41 (13.02~18.5); average age is 9.68±1.77 years old (7.0~13.0 years). There was significant difference in BMI between the two groups (P=0.000). There was no significant difference in age or gender between the two groups (P>0.05) (**Table 3**).

Expression of LXR, COX-2 and CETP mRNA between normal and obese children

The relative expression of LXR mRNA, COX-2 mRNA and CETP mRNA between normal and obese children were compared (**Figure 1**). The expression levels of LXR mRNA, COX-2 mRNA and CETP mRNA in the obese children were 9.141±11.480, 6.033±5.759, and 7.363±10.618, respectively. Compared with the control group, the expression levels of LXR mRNA, COX-2 mRNA and CETP mRNA in the obese group were significantly higher than that in the control group, and the difference was statistically significant (P<0.05). Correlation analysis showed that LXR and COX-2 were positively correlated (r=0.589, P<0.05). LXR and CETP were positively correlated (r=0.684, P<0.05).

Expression of LXR, COX-2 and CETP mRNA between boys and girls in obese children

The obese children were divided into boy group and girl group according to the gender. The expression levels of LXR mRNA, COX-2 mRNA and CETP mRNA in boys were 9.18±12.40, 5.98±5.82 and 7.80±1.47 respectively, and those in girls were 8.96±5.65, 6.27±5.64 and 5.30±4.70, respectively. The expression of LXR mRNA, COX-2 mRNA and CETP mRNA in boys were not significantly higher than those in girls (P>0.05) (**Figure 2**).

Comparison of serum aminotransferase and blood lipid levels

In obese children, all the levels of AST, ALT, GGT, CHOL, TG and LDL-C were higher than those in normal children (P<0.05) (**Table 3**).

Correlation analysis and logistic regression analysis of increased LXR mRNA

The expression of LXR was positively correlated with AST, ALT, CHOL, LDL-C and BMI (r=0.18-0.26, P<0.05, **Table 3**).

LXR regression analysis was carried out by using LXR>1 as the dependent variable, and

Table 2. Multivariate logistic regression analysis of the risk factors for sleeping disorders

	B	SE	Wald	Sig	Exp (B)	95% CI
Weight	1.578	0.125	158.888	0	4.848	3.793~6.196
Irregular sleep	1.480	0.114	169.180	0	4.393	3.515~5.490
Not enough sleeping time	1.118	0.141	63.322	0	3.059	2.323~4.029
Sleeping with their parent	1.202	0.125	93.123	0	3.328	2.603~4.253
The time of going to bed of fosterer	0.909	2.232	15.377	0	2.481	1.575~3.908
Adenoids	0.894	0.159	31.673	0	2.444	1.790~3.336
Watching nervous TV before 30 min to sleep	0.801	0.249	10.329	0.001	2.228	1.367~3.631
Acute exercise before 30 min to sleep	0.688	0.271	6.431	0.011	1.990	1.169~3.388
The bedroom with TV	0.524	0.242	4.693	0.030	1.689	1.051~2.713
Anxiety of the father	0.327	0.150	4.781	0.029	1.387	1.034~1.850
The parents' bad marriage	0.371	0.184	4.073	0.044	1.449	1.011~2.078

Table 3. General data and the metabolic indexes detection in obesity and normal controls, the correlation analysis of AST, ALT, CHOL, LDL-C and BMI with LXR, and multivariate logistic regression analysis of the risk factors for LXR>1

	Obesity (n=80)	Normal (n=51)	P	Correlation with LXR		Multivariate logistic regression analysis			
				R	P	β	S.E.	OR (95% CI)	P
Age	9.45±1.78	9.68±1.77	0.478						
Gender			0.874 (χ^2=0.025)						
Boy	66	42							
Girl	14	9							
AST (IU/L)	27.94±13.96	22.86±4.22	0.003	0.176	0.044	0.073	0.034	1.076 (1.006~1.150)	0.032
ALT (IU/L)	36.76±39.32	14.55±5.887	0	0.198	0.023	0.035	0.015	1.036 (1.007~1.066)	0.015
GGT (IU/L)	24.16±32.41	14.36±2.96	0	0.122	0.168	0.059	0.033	1.06 (0.994~1.131)	0.077
CHOL (mmol/L)	3.96±0.67	3.67±0..83	0.04	0.23	0.008	0.712	0.286	2.038 (1.164~3.567)	0.013
TG (mmol/L)	1.20±0.51	0.76±0.34	0	0.152	0.084	0.709	0.415	2.032 (0.972~4.584)	0.087
HDL-C (mmol/L)	1.12±0.20	1.31±0.27	<0.000	-0.003	0.971	-0.027	0.757	0.973 (0.221~4.290)	0.971
LDL-C (mmol/L)	2.15±0.58	1.75±0.47	<0.000	0.194	0.027	0.777	0.357	2.176 (1.082~4.376)	0.029
BMI	23.60±3.71	16.63±2.41	<0.001	0.262	0.002	0.123	0.042	1.131 (1.042~1.228)	0.003

aminotransferase, blood lipid and BMI as the independent variables. CHO≥5.20 mmol/L (OR=2.038), LDL-C≥3.36 mmol/L (OR=2.176), ALT≥40 IU/L (OR=1.036), and BMI≥18.9 kg/m2 (OR=1.131) were the risk factor of LXR>1 (P<0.05, **Table 3**).

Discussion

Adequate sleep is the key to ensure the healthy development of children's physical and mental health. Long-term lack of sleep, memory, comprehension, judgment will be seriously damaged, eventually leading to significant decrease in learning efficiency and creative thinking [21]. This study shows that the average sleep time of pupils in Lanzhou, China is 9.29±0.92 h, which is less than 10 h required by the Ministry of Education. The sleep time of pupils in different age groups decreased gradually with age, which was in accordance with the conclusion of the literature [22-24]. The increase of sleep time with the grade of 10 years (grade 3) was significantly reduced, possibly related to the gradual increase of academic burden. In addition to sleep, with age, weight loss increased, the same bedroom with their parents, recent family accidents, living room environment, and dependents of education, occupation and bedtime directly affect the child's sleep time, indicating high Career pressure on the child's sleep have a negative impact. Part of the primary school students do not sleep also caused lack of sleep, due to the 8 am~6 pm working hours at Lanzhou City, so that the nursing people must be on time to wake up their children to school. Parents and family work far away, the child lunch and nap will solve in a "small table",

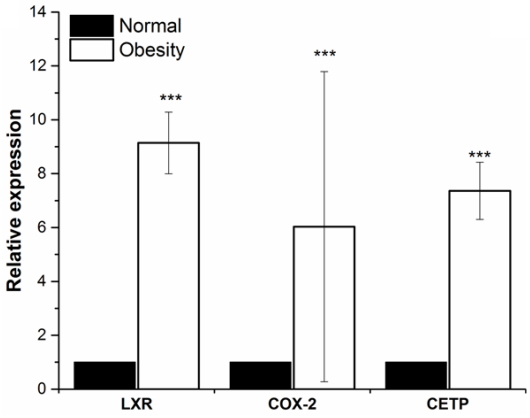

Figure 1. The relative expression of LXR mRNA, COX-2 mRNA and CETP mRNA between normal and obese children were compared. ***P<0.001.

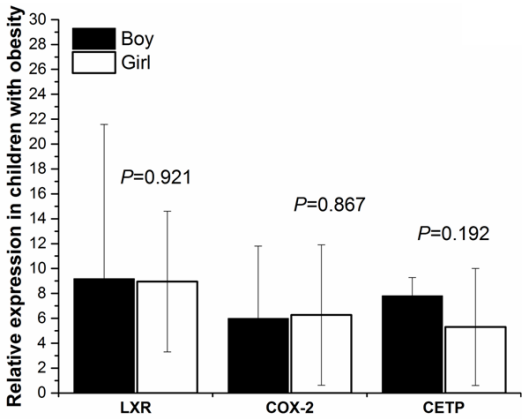

Figure 2. Expression of LXR, COX-2 and CETP mRNA between boys and girls in obese children.

where the environment is often noisy, a poor quality don't do not even take a nap. And the overall sleep time was late due to the leave school delay in the afternoon.

The incidence rate of sleep disorders was 16.24% in Lanzhou, China, which is lower than that another report that studied the sleep disorders in 2-16 years olds in Lanzhou, but is consistent with the 10%~45% in other studies [25, 26]. The incidence of sleep disorders in boys was higher than that in girls, among which snoring and restless sleep were statistically significant, which may be related to the active character of boys. Among the risk factor, besides the common factors such as weight, irregular sleep, not enough sleeping time and adenoids, other factors such as sleeping with their parent, the time of going to bed of fosterer, watching nervous TV before 30 min to sleep, acute exercise before 30 min to sleep, the bedroom with TV, anxiety of the father, and the parents' bad marriage were also important risk factors. In addition, Lanzhou City is located in high-altitude areas that may also affect the quality of sleep. The incidence of sleep disorders in this study is slightly lower than some of the developed cities, may be due to that Lanzhou is located in the economically backward western areas with low pressure, as well as the social and cultural differences. Parents with high education is one of the main factors affecting students sleep, indicating the influence of highly educated parents working pressure on the child's sleep cannot be ignored. How to coordinate the relationship between the pressure in the process of social development and the health of the children sleep should arouse our attention.

The increasing number of obese children has become a global public problem. Epidemiological and clinical studies have shown that the association between obesity and cardiovascular disease has begun in early life [7, 8]. Macrophages play an important role in lipid metabolism and inflammatory response, and are the main factors in the pathogenesis of atherosclerosis. LXR is a lipid dependent regulator in the expression of inflammatory genes, which may be a link between the function of lipid metabolism and the function of macrophages in the lipid metabolism [27]. At present, the treatment of non-alcoholic fatty liver disease, atherosclerosis and other diseases targeted LXR are increasing [28, 29]. Pharmacological studies confirm that treatment the low level of LXR is an effective strategy for anti-atherosclerosis in mice [30]. In recent years, more and more researches have been studied the roles of LXR in the adult inflammatory reaction and abnormal lipid metabolism, but is lacking in children. In this study, we found the expression levels of mRNA LXR, mRNA COX-2 and mRNA CETP in obese children were higher than those of normal weight children.

The expressions of LXR, COX-2 and CETP mRNA were significantly correlated with the degree of obesity. The expression of LXR, COX-2 and CETP mRNA in obese children was significantly higher than that in normal children. Obesity can lead to liver damage and lipid disorders. ALT, CHOL, LDL-C and BMI were significantly corre-

lated with LXR level. Expression of LXR, COX-2 and CETP mRNA was not influenced by children's gender. The increase of AST, ALT, CHOL; BMI, LDL-C can lead to increased LXR expression. In the prevention and treatment of liver dysfunction and dyslipidemia caused by obesity in school age children, the focus on the activation of LXR in early stage may improve the outcome.

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Disclosure of conflict of interest

None.

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