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Original Article

Positive correlations between and prediction of FGF21, adiponectin, leptin and NPY concentrations in the cerebrospinal fluid of Chinese subjects using back propagating artificial neural networks

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Abstract: Background and aims: The hepatokine fibroblast growth factor 21 (FGF21) is induced in patients with metabolic diseases. FGF21 is part of a complex network of hormones that includes adiponectin, leptin and neuropeptide Y (NPY). This network modulates energy metabolism, particularly glucose and lipid metabolism. Nevertheless, our understanding of these hormones and their interrelationships in different organs remains incomplete. The current study investigated relationships between the metabolic regulators FGF21, adiponectin, leptin and NPY in the cerebrospinal fluid (CSF) of Chinese subjects. Materials and methods: Sixty-nine subjects (37 males and 32 females) were recruited for this study. The CSF levels of FGF21, adiponectin, leptin and NPY were measured in all patients by radioimmunoassay. Results: Significant differences were not observed between male and female subjects in the CSF levels of FGF21, adiponectin, leptin and NPY. However, our measurements indicate the existence of positive linear correlations between the CSF concentrations of these metabolic regulators. Conclusions: The CSF concentrations of each of the metabolic regulators investigated in this study could be predicted using the concentrations of the other three regulators and back propagation artificial neural networks (BP-ANN). Our observations have important implications for our current understanding of these molecules. Additionally, these findings may serve as the basis for future analysis of the roles played by these metabolic regulators in hormonal network regulation in the central nervous system.

Keywords: Back propagation artificial neural networks, cerebrospinal fluid, fibroblast growth factor 21, adiponectin, leptin, neuropeptide Y, energy metabolism, metabolic diseases

Introduction

Energy homeostasis regulation is an important central nervous system (CNS) function that coordinates adaptive responses to environmental and physiological perturbations to maintain and support good health. A complex network of hormones is essential for the maintenance of energy homeostasis in the body. Fibroblast growth factor 21 (FGF21), adiponectin, leptin and neuropeptide Y (NPY) are components of a hormone network that controls carbohydrate and lipid metabolism [1-6]. FGF21, a 181 amino acid member of the FGF protein superfamily, acts as a metabolic hormone with anti-hyperglycemic, anti-hyperlipidemic and thermogenic activities [5, 6]. Its expression and activity is governed by nutritional status and metabolic stress [5, 6]. Increased concentrations of circulating FGF21 have been linked to metabolic diseases, including insulin-resistant states, type 2 diabetes and obesity [5]. Several studies suggest that FGF21 plays this pivotal metabolic role through the control of several other hormones, including adiponectin, leptin and NPY [7, 8]. For instance, FGF21 treatment

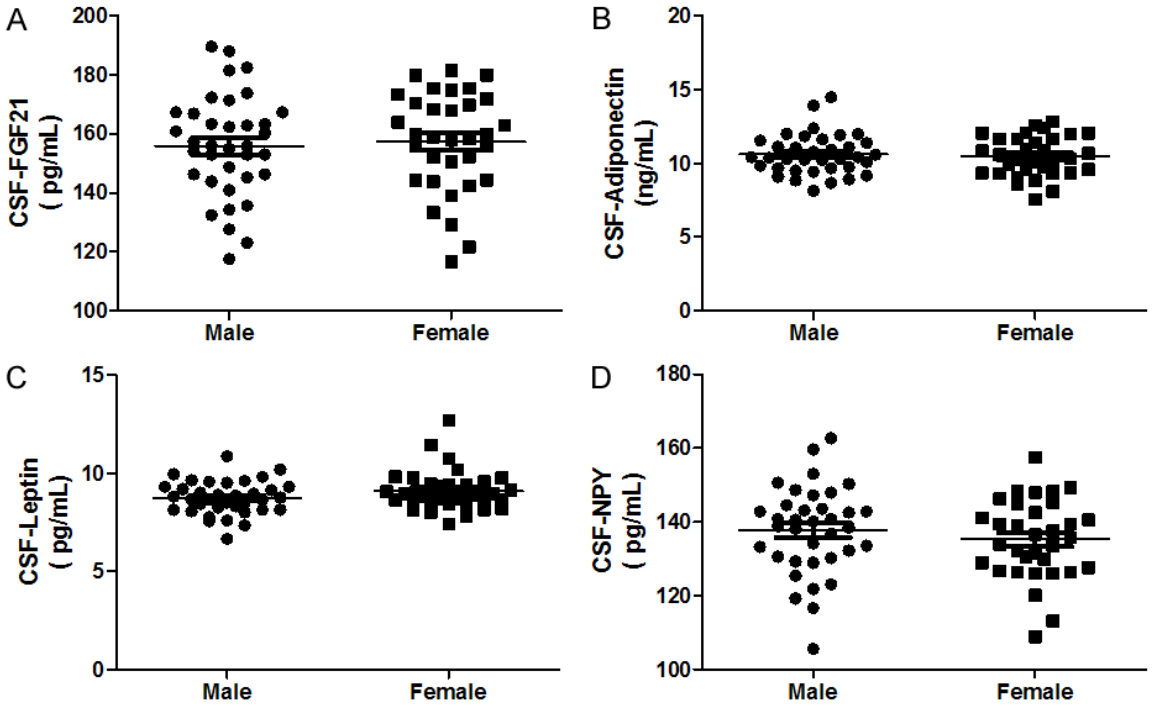

Figure 1. The concentration of FGF21, adiponectin, leptin and NPY in CSF. FGF21 (A), adiponectin (B), leptin (C) and NPY (D) concentrations in the CSF of 69 Chinese subjects were measured using commercial radioimmunoassay kits. No sex differences were found for CSF FGF21, adiponectin, leptin or NPY levels.

leads to profound increases in the concentration of circulating adiponectin, suggesting that FGF21 positively regulates adiponectin secretion. Additionally, adiponectin release from adipose tissue is required for the glucose/insulin-lowering action of FGF21 [7]. Similarly, functional leptin signaling is required for the body-weight-lowering effect of FGF21 [9]. However, the precise mechanisms by which FGF21 increases energy expenditure and promotes bodyweight loss are unknown.

The brain plays a central role in controlling carbohydrate and lipid metabolism. FGF21 (which is produced in the liver) can cross the blood-brain barrier. Thus, it has been proposed that FGF21 may act as a link between the brain and peripheral metabolic tissues [10, 11]. Intracerebroventricular infusion of FGF21 increases food intake, energy expenditure and hepatic insulin sensitivity in obese rats [12]. Similarly, studies using tissue-specific FGF21 knock out mice have reported that FGF21 acts on the CNS to reduce energy expenditure and body weight in obese mice [12]. These data strongly suggest that the metabolic effects of FGF21 are mediated, at least in part, through the CNS. Moreover, it has been proposed that FGF21 induces torpor. Torpor is the murine equivalent of hibernation. It is an adaptive response to environmental pressures, and is characterized by a reduced metabolic rate. Both transgenic expression and administration of FGF21 in mice stimulates torpor [13]. Similarly, intracerebroventricular injection of NPY induces torpor in hamsters [14]. It is possible that FGF21 may promote torpor by inducing the expression of NPY [15]. However, there is currently no direct evidence demonstrating that FGF21 acts as an upstream regulator of NPY. Despite the fundamentally important biological roles of FGF21 in the central and peripheral hormone networks, our understanding remains incomplete concerning this metabolic network's control of energy metabolism and hormone cooperation within different organs.

Artificial neural networks are computational models inspired by the system of interconnected neurons in the CNS. These models are capable of machine learning and pattern recognition and are used to predict the function and correlation of a large number of inputs of previously unknown interdependence. Back propagation,

Table 1. Correlations of CSF FGF21, adiponectin, leptin or NPY levels with anthropometric parameters

Variables	All Subjects (69)	CSF-FGF21 (pg/mL)		CSF-Adiponectin (ng/mL)		CSF-Leptin (pg/ml)		CSF-NPY (pg/mL)	
	Median	r	P	R	P	r	P	r	P
Age (years)	30.87 ± 9.26	0.063	0.622	-0.044	0.715	0.054	0.658	-0.064	0.601
Weight (kg)	68.75 ± 15.60	-0.082	0.501	0.011	0.927	-0.65	0.598	0.069	0.572
Height (m)	1.69 ± 0.08	0.075	0.540	0.063	0.608	-0.071	0.564	0.112	0.361
BMI	23.88 ± 4.09	-0.159	0.192	-0.026	0.833	-0.052	0.671	0.027	0.828
CSF-Leptin (pg/mL)	8.91 ± 0.97	0.313	0.009*	0.334	0.005*	-	-	0.301	0.012*
CSF-Adiponectin (ng/mL)	10.55 ± 1.37	0.478	< 0.0001*	-	-	0.334	0.005*	0.292	0.015*
CSF-NPY (pg/mL)	136.55 ± 11.34	0.304	0.011*	0.292	0.015*	0.301	0.012*	-	-
CSF-FGF21 (pg/mL)	156.52 ± 17.01	-	-	0.478	< 0.0001*	0.313	0.009*	0.304	0.011*

Pearson's correlation coefficient (r) and the probability value of significance (P) are shown. *P < 0.05.

which is used in conjunction with optimization methods such as gradient descent, is a commonly used method of training artificial neural networks to compute function approximations [16]. In this study, the back propagation artificial neural networks (BP-ANN) algorithm was used to develop a concentration-predicting model for FGF21, adiponectin, leptin and NPY that uses the measured concentrations of three of these molecules in the cerebrospinal fluid (CSF) as input variables to predict the concentration of the fourth molecule. Although FGF21, adiponectin, leptin and NPY are all detectable in human CSF, it is unknown whether they comprise a co-regulated hormonal network in the CNS that modulates energy metabolism. Therefore, we measured the concentrations of FGF21, adiponectin, leptin and NPY in the CSF of 69 Chinese subjects, analyzed the data to determine if there were any associations among these regulators and developed a model to predict their concentration in the CSF.

Materials and methods

Subjects

Sixty-nine subjects (n = 37 males; n = 32 females) were recruited from a patient population undergoing surgery in the Beijing Jishuitan Hospital for lower extremity injuries due to ligament damage or bone fractures below the knee. The volunteer subjects had no history of drug abuse or dependence, including alcohol or nicotine abuse. Patient drug use was self-reported and confirmed by relatives. Participants with a family history of psychiatric disorders and neurological diseases, as determined by the Mini-International Neuropsychiatric Interview, Chinese version, were excluded from the study. Individuals with systemic or CNS diseases were also excluded from this study. All participants were Chinese, with an age range of 17 to 50 years. The study was approved by the Institutional Review Board of Beijing Jishuitan Hospital. For all participants, informed written consent was either obtained directly or obtained from consenting guardians on behalf of the participant.

CSF collection

Lumbar puncture was performed under sterile conditions by a licensed anesthetist with the subject positioned in the lateral decubitus position. CSF was drawn under spinal anesthesia before surgery. The spinal needle was inserted into the L3/L4 or L4/L5 interspace and a 5 mL CSF sample was obtained. Each CSF sample was separated into 0.5 mL fractions in polypropylene tubes and immediately frozen at -80°C until analysis.

CSF measurement of FGF21, adiponectin, leptin and NPY

CSF sample quantification of FGF21, leptin, NPY and adiponectin protein levels was performed using commercial radioimmunoassay kits (Phoenix Pharmaceuticals, Belmont, CA, USA; detection limits: 230 ng/mL for FGF21, 104 pg/mL for leptin and 26 pg/mL for NPY; and Millipore, St. Charles, Missouri, USA; detection limit: 1 ng/mL for adiponectin). Ten percent of each CSF sample (0.5 mL) was assayed in duplicate.

BP-ANN model

The concentrations determined for FGF21, adiponectin, leptin and NPY in the CSF of the 69

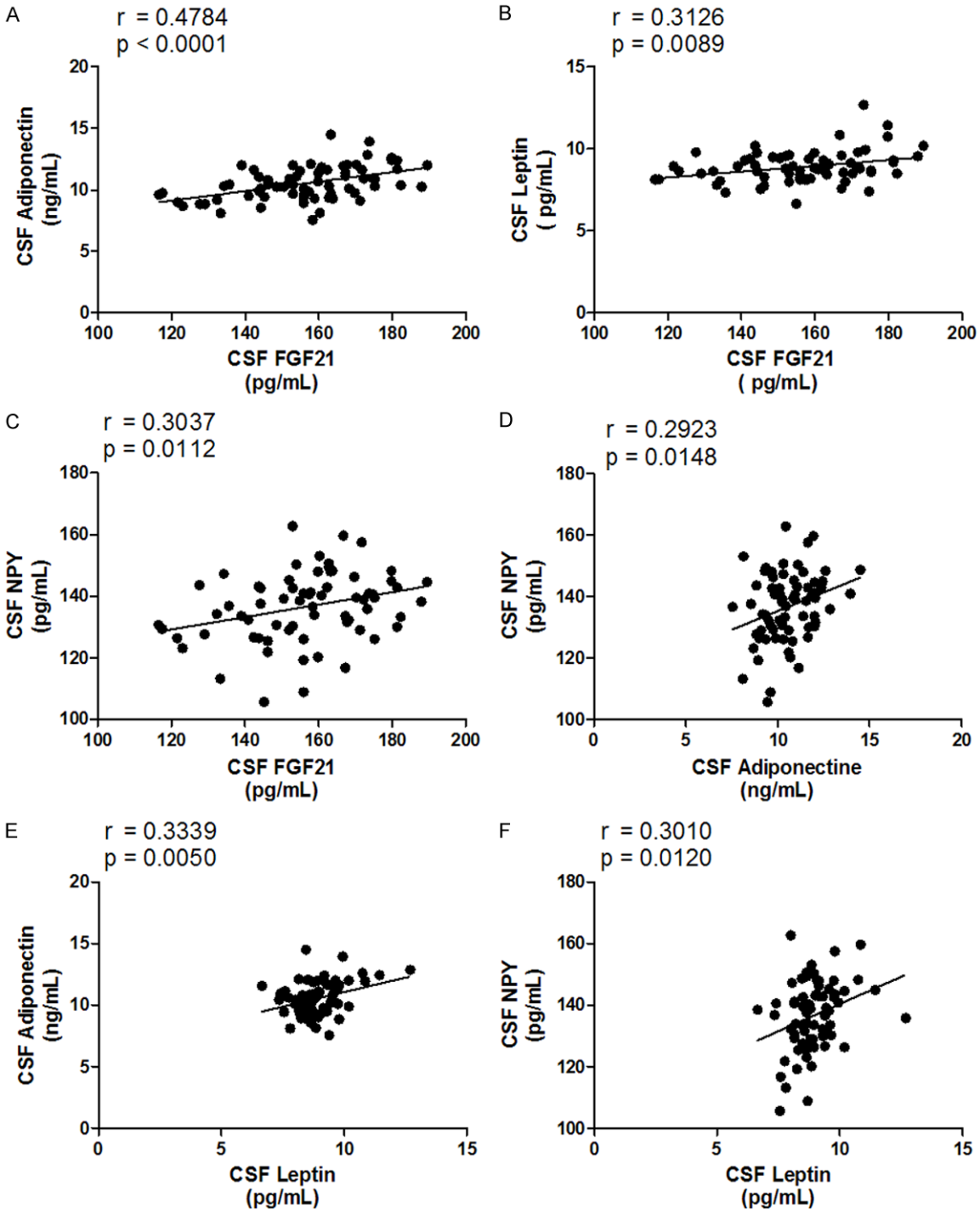

Figure 2. Correlation between FGF21, adiponectin, leptin and NPY concentrations in CSF. Pearson's correlation coefficient (r) was calculated to test the correlations between FGF21, adiponectin, leptin and NPY concentrations. A highly significant, positive, linear correlation was identified between the CSF levels of FGF21 and adiponectin (r = 0.478, P < 0.0001) (A), FGF21 and leptin (r = 0.313, P = 0.009) (B) and FGF21 and NPY (C) (r = 0.304, P = 0.011). CSF adiponectin levels were positively correlated with NPY (r = 0.292, P = 0.015) (D) and leptin (r = 0.334, P = 0.005) (E). CSF leptin levels were correlated with NPY (r = 0.301, P = 0.012) (F).

subjects were used as input data for BP-ANN. The input layer consisted of three factors and the output layer consisted of one factor. For instance, when adiponectin, leptin and NPY

Table 2. The BP-ANN model fitness index for FGF21, adiponectin, leptin and NPY in a population of 69 Chinese subjects

Index	FGF21	Adiponectin	Leptin	NPY
Mean squared error	0.0014982	0.0014516	0.0014992	0.0014985
The magnitude of the gradient	0.00133	0.013264	0.020203	0.010269
Validation checks	0	0	0	0
Correlation coefficient (r)	0.99650	0.99524	0.99251	0.99519

concentrations were selected as the input layer, then the output layer represented FGF21 concentrations. As previously described, the numbers of nodes in the hidden layer (the nodes between the input and output layers where the actual processing is performed) were based on the formula $m = \sqrt{n + l} + a$, where m is the number of nodes in the hidden layer, n is the number of nodes in the input layer, l is the number of nodes in the output layer and a is a constant from 1 to 10 [17]. The transfer function of the hidden layer nodes was tansig, and the output was purelin. Tansig is the hyperbolic tangent sigmoid transfer function, and purelin is the linear transfer function. These transfer functions calculate a layers output value from its net input value. BP-ANN analysis was performed using the Matlab R2011a software (Matworks, Natick, MA, USA).

Statistical analysis

Statistical analysis was performed using the SPSS software version 17 (SPSS Inc. Chicago, IL, USA). The normal distribution of the indexes of CSF hormone levels was determined using the One-Sample Kolmogorov-Smirnov test. The linear correlation of parameters of CSF hormone levels was analyzed using Pearson's correlation test. A two-tailed $P < 0.05$ was considered statistically significant.

Results

FGF21, adiponectin, leptin and NPY concentrations in the CSF of Chinese subjects

The CSF concentrations of FGF21, adiponectin, leptin and NPY were measured using commercial radioimmunoassay kits. No sex differences were found in FGF21, adiponectin, leptin or NPY levels (**Figure 1**). The FGF21, adiponectin, leptin and NPY concentrations measured in the current study were in agreement with previous studies [18-20]. **Table 1** shows the CSF FGF21, adiponectin, leptin and NPY concentrations, anthropometric parameters and body mass indexes (BMI) of all subjects and their respective associations. Pearson's correlation analyses yielded no correlation between FGF21, adiponectin, leptin or NPY levels and age, weight, height, gender or BMI (**Table 1**). However, FGF21, adiponectin, leptin and NPY CSF concentrations were positively correlated with one another. Pearson's correlation coefficient (r) values were between 0.3 and 0.5 for the CSF concentrations of FGF21, adiponectin, leptin and NPY (**Figure 2**). A highly significant, positive correlation was identified between the CSF levels of FGF21 and adiponectin ($r = 0.478$, $P < 0.0001$), FGF21 and leptin ($r = 0.313$, $P = 0.009$) and FGF21 and NPY ($r = 0.304$, $P = 0.011$). CSF adiponectin showed a positive linear correlation with leptin ($r = 0.334$, $P = 0.005$) and NPY ($r = 0.292$, $P = 0.015$). Finally, CSF leptin was positively correlated with NPY ($r = 0.301$, $P = 0.012$) (**Figure 2** and **Table 1**).

Development of a BP-ANN prediction model to predict CSF FGF21, adiponectin, leptin and NPY concentrations

Once the BP-ANN model for FGF21, adiponectin, leptin and NPY concentration prediction in CSF was established, the training goal was accomplished within 1000 training cycles (epoch = 1000). The mean square error (MSE), magnitude of the gradient, number of validation checks and the correlation coefficients demonstrating the successful development of the model are listed in **Table 2** and **Figure 3**. The MSE was the average squared error between the network outputs and the target and represented the default performance function of feed-forward networks. The correlation coefficient was used to assess the relationship between the predicted and measured concentrations [21]. Therefore, the correlation coefficient was used to predict individual CSF hormone concentrations by using the concentra-

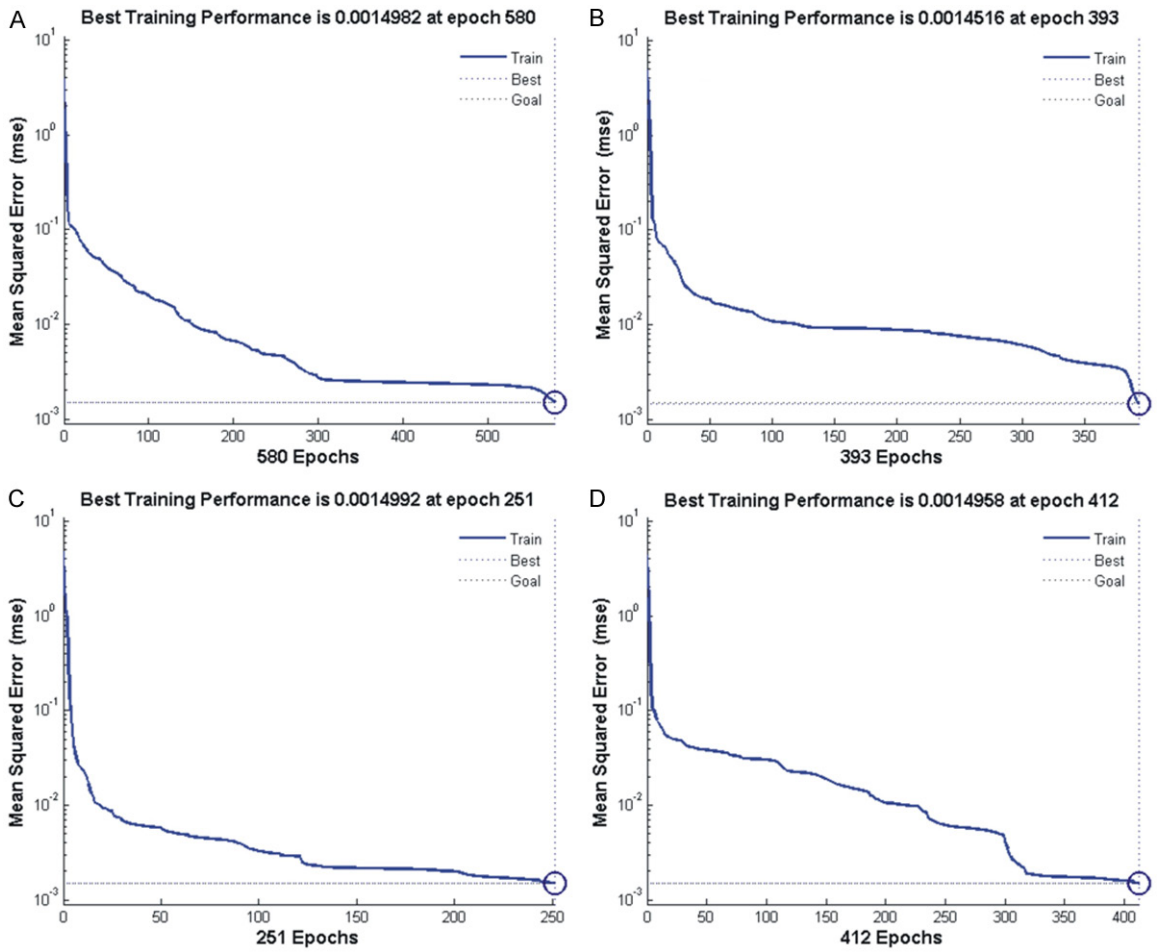

Figure 3. The training BP-ANN model. The best training performance for the prediction of FGF21 (A), adiponectin (B), leptin (C) and NPY (D) achieved in the BP-ANN model as measured by the mean square error (mse). The number of Epochs (the steps in the training process of the artificial neural network) necessary for reaching the best/goal concentration is shown.

tions measured for the other three members of the hormonal network as input. The established BP-ANN model was employed to predict the CSF concentrations of FGF21, adiponectin, leptin and NPY in the study population. The predicted concentration values generated by BP-ANN were in agreement with the CSF concentrations previously measured for the hormonal network (**Figure 4**).

Discussion

FGF21, adiponectin, leptin and NPY are part of a complex hormonal network that controls the body's energy homeostasis, including carbohydrate and lipid metabolism [22]. These metabolic regulators are all detectable in human CSF [18-20, 23, 24], but their interactions and functions in the CNS remain obscure. In this study, we measured CSF FGF21, adiponectin, leptin and NPY concentrations in a population of 69 Chinese subjects. In agreement with previous studies, no sex differences were found in the CSF levels of FGF21, adiponectin, leptin or NPY [18-20]. Similarly, no correlations were found between anthropometric parameters and the CSF concentrations of FGF21, adiponectin, leptin or NPY. In contrast, a previous study reported that CSF FGF21 levels, but not CSF adiponectin levels, were positively correlated with both BMI and body weight [19]. The main cause of disagreement between this previous study and ours may arise from the smaller sample size of their study and the heavier BMI distribution of their study population. Thirty-eight Caucasian subjects participated in the earlier study. Fourteen of these participants

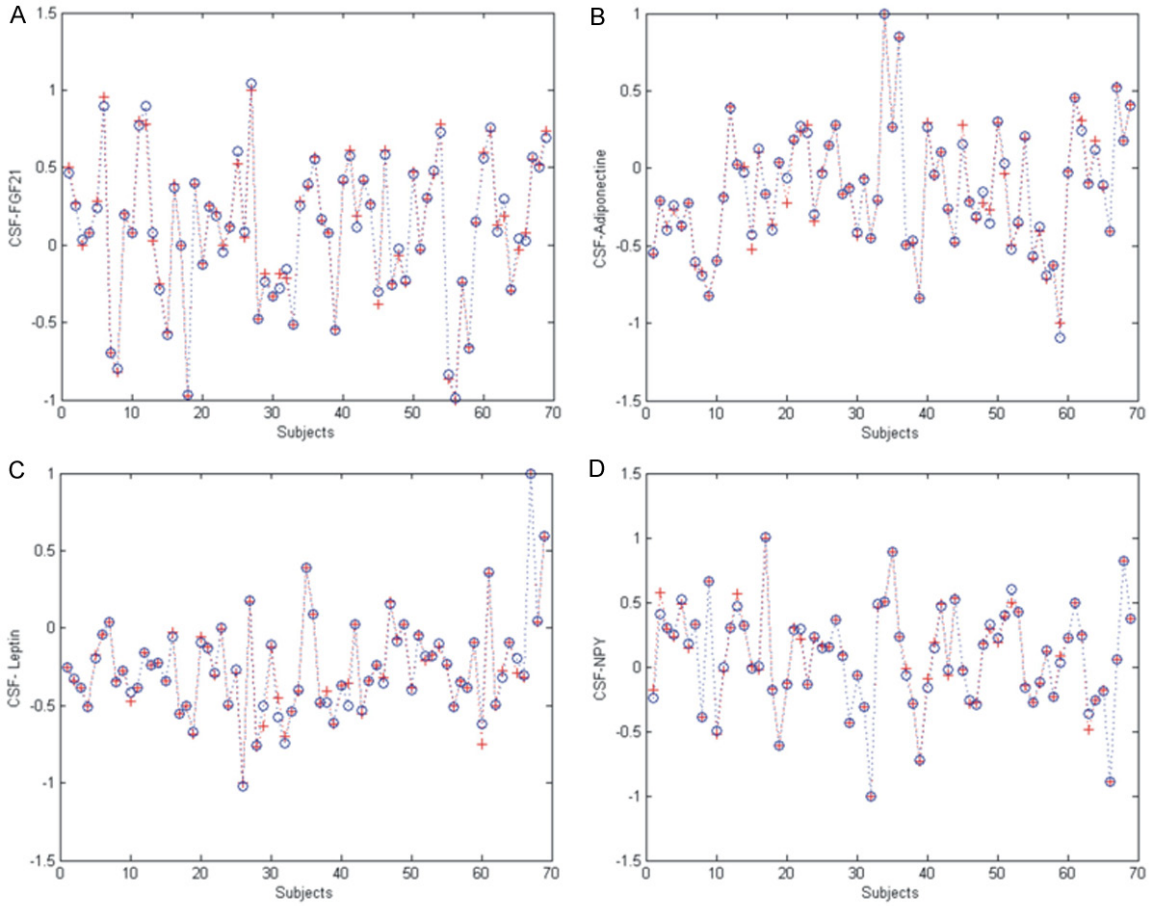

Figure 4. The measured and predicted CSF concentrations of FGF21, adiponectin, leptin and NPY. The measured ("+") and predicted ("o") CSF concentrations of FGF21 (A), adiponectin (B), leptin (C) and NPY (D) in a population of 69 Chinese subjects. The y-axis shows the relative concentrations of the measured and predicted relative CSF concentrations of FGF21, adiponectin, leptin and NPY.

had normal body weight, 14 subjects were overweight (BMI 25 to < 30 kg/m^2), and 10 subjects were obese (BMI > 30 kg/m^2). In our study, out of 69 patients, 48 had normal body weight, 15 were overweight and just 6 were obese. Therefore, only 37% of the subjects in the earlier study fell within the normal BMI range, while, in contrast, 70% of our subjects had a healthy BMI. Since obesity is known to affect FGF21 concentrations, the differences in BMI distribution may explain the observed discrepancies between the two studies.

Using Pearson's correlation analyses, we demonstrated a positive association between the CSF concentrations of the metabolic regulators FGF21, adiponectin, leptin and NPY, indicating that they form an interconnected functional network of hormones participating in energy homeostasis regulation in the CNS. The significant positive correlation we observed led us to develop a BP-ANN model capable of predicting the concentrations of FGF21, adiponectin, leptin and NPY in CSF. Once established, the BP-ANN model quickly reached the training goal and exhibited a high correlation coefficient ($r > 0.99$). Although several newer methods of artificial mathematical modeling, such as SVM (Support Vector Machine) or ELM (Extreme Learning Machine), have been reported recently [25, 26], BP-ANN is still one of the most powerful and widely used artificial modeling methods and can be applied to a variety of biomedical questions [27, 28]. In the future, the BP-ANN model for FGF21, adiponectin, leptin and NPY will be a useful tool for predicting the CSF concentrations of these proteins. This model will also aid future investigations of this regulatory

network and its biological significance in the CNS.

Our study had a number of limitations that should be taken into consideration. Although our study investigated a larger patient population than an earlier similar study, our sample size was still relatively small. A larger sample size should be used in future investigations. Second, three of the subjects enrolled in our study were under 18 years of age (one male, two females). The young age of these subjects may have influenced their CSF protein levels. Therefore, future studies should include an age limit as a subject selection criterion.

The role of FGF21 and its associated hormonal network in the CNS remains unclear; however, the pharmacological actions and physiological roles of the metabolic regulators in this network make FGF21 and its associated proteins attractive drug candidates for the treatment of various metabolic diseases [29]. Further studies will be needed to understand the regulation of the FGF21 hormonal network in the CNS as well as this network's role in the regulation of energy homeostasis.

Acknowledgements

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Disclosure of conflict of interest

None.

Abbreviations

CNS, central nervous system; FGF21, Fibroblast growth factor 21; CSF, Cerebrospinal fluid; NPY, Neuropeptide Y; BP-ANN, back propagation artificial neural networks.

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