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Selective cerebral overexpression of growth hormone alters cardiac function, morphology, energy metabolism and catcholamines in transgenic mice

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Abstract

Background: Growth hormone (GH) has important regulatory effects on cardiac morphology and function both during normal development as well as in pathophysiological settings such as myocardial infarction (MI) and congestive heart failure (CHF). In order to investigate in more detail the interaction between GH and sympathetic nervous system (SNS) system we studied the effects of selective cerebral GH overexpression on myocardial content of catecholamines, myocardial and brain energy metabolism as well as on cardiac function during resting and stress conditions in a transgenic mouse model.

Methods: Transgenic mice with selective bovine GH overexpresssion under control of glial fibrillary acidic protein promoter in the brain (GFAP-bGH, $n = 15$) were created and compared to genetically matched non-transgenic mates (Control, $n = 15$). Cardiac morphology and function were evaluated in vivo using transthoracic echocardiography during resting and stress conditions induced pharmacologically by dopamine (D) and isoprotenolol (ISO). Myocardial and brain energy metabolism were evaluated non-invaseively using in vivo volume-selective phosphorus magnetic resonance spectroscopy (^{31}P MRS). Myocardial content of catecholamines was analyzed by means of HPLC.

Results: Compared to the C animals, the GFAP-bGH mice have showed several differences in the cardiac phenotype. Systolic (fractional shortening) and diastolic function (*E*/*A* wave ratio of mitral flow) was disturbed in the GFAP-bGH mice (both $p < 0.05$). During the dopamine stress, there was chronotropic insufficiency in the GFAP-bGH group ($p < 0.01$) while no difference was observed in response to isoprotenolol. Left ventricular dimensions were increased in GFAP-bGH mice ($p < 0.05$). There was a tendency for higher body weight in GFAP-bGH compared to the control group ($p = 0.06$) while no difference was observed in heart weight and brain weight when normalized for body weight. Myocardial content of noradrenaline was lower in the GFAP-bGH group ($p < 0.05$). PCr/ATP ratio was higher ($p < 0.05$) in the brain and lower in the heart ($p < 0.05$) in the GFAP-bGH mice.

Conclusions: Selective cerebral overexpression of GH results in alterations of cardiac function, morphology and metabolism in transgenic mice. Decreased myocardial content of catecholamines in the GFAP-bGH mice suggests central interaction between GH and sympathetic nervous system.
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Keywords: Growth hormone; Myocardial energy metabolism; 31P magnetic resonance spectroscopy; Transgenic mice

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1. Introduction

Growth hormone (GH) exerts important physiological and pathophysiological effects on the heart [1]. It has been known for a long time that patients with GH deficiency [2] and GH excess [3,4] have numerous abnormalities in cardiac function and morphology. This awareness has motivated researchers to investigate closer the interaction between GH and the heart. Increasing knowledge from basic research suggest that GH (and its mediator insulin-like-growth factor I) is involved in the regulation of many different cellular and subcellular processes in the myocardium. This have given rise to the idea to use GH in the treatment of pathological conditions such as myocardial infarction (MI) and congestive heart failure (CHF). Consequently, many experimental studies have demonstrated positive effects of GH treatment on cardiac function and remodeling in animal models of MI and CHF [5,6]. These beneficial effects of GH in the experimental settings have been translated to the certain extent even in recent clinical trials with CHF patients although these results are not always consistent [7,8].

Chronic neurohormonal overactivation is regarded as one of the most important etiopathogenic factors in development and progression of CHF. Particularly overactivation of the sympathetic nervous system (SNS) contributes to infliction of a continuous myocardial damage and progression of pathologic cardiac remodeling.

In the previous study, we have reported that GH improves cardiac function and energy metabolism while at the same time it attenuates pathologic remodeling [9]. These findings were associated with unexpected decrease in myocardial concentration of noradrenaline (NA) suggesting important interaction between GH–IGF system and the sympathetic nervous system (SNS). The mechanisms behind interaction between GH and sympathetic system are not well-known. In principle, GH could interact with SNS at the central level, peripheral level or both.

In order to investigate in more detail the interaction between GH and SNS system we studied the effects of selective cerebral GH overexpression on myocardial content of catecholamines, myocardial and brain energy metabolism as well as on cardiac function during resting and stress conditions in a transgenic mouse model. The results presented in this paper add further evidence to the important and complex role of GH in the regulation of cardiac and brain phenotype.

2. Methods

2.1. Animals

To generate GFAP-bGH transgenic animals 110 injected C57 BL/6JxCBA embryos were implanted into 5 C57 BL/6JxCBA foster mothers resulting in 22 new born mice. Five mice were identified carrying GFAP-bGH transgene (founder animals) using Southern blot analysis and were allowed to reproduce. The expression of GH was constructed to be under control of glial fibrillary acidic protein promoter that is generally expressed in astrocytes throughout the brain. The environment of the animal rooms was controlled with a 12-h light–dark cycle (07.30 AM–07.30 PM, with a 1-h dawn/sunset function), a relative humidity between 45% and 55% and a temperature of 20 °C. The mice had free access to tap water and standard pellet chow (R-34, Lactamin, Vadstena, Sweden). The study was performed after prior approval from the local ethical committee for animal experimentation at the Göteborg University, Sweden. At 23 weeks of age 15 female GFAP-bGH transgenic mice and 15 genetically matched control mice were randomly selected for the purpose of this study. After in vivo investigations, the animals were sacrificed, organs were collected and immediately frozen in liquid nitrogen for future analysis.

2.2. In vivo volume-selective ^{31}P MRS of heart and brain

Five female GFAP-bGH and five female control mice, were randomly selected for heart and brain ^{31}P MRS. The MR imaging and spectroscopy experiments were performed on a 2.35 Tesla (T) horizontal magnet with a 20-cm bore (Bruker Biospec 24/30) interfaced with an X-32 acquisition system giving operating frequencies for ^{1}H and ^{31}P MR 100 and 40.5 MHz, respectively. The experiments were performed according to the procedure as previously described [10]. The size of the volume of interest (VOI) for cardiac spectroscopy was $8 \times 4 \times 4$ mm^3 (128 μL, Figs. 1 and 2) and for brain spectroscopy $7 \times 4 \times 4$ mm^3 (112 μL, Figs. 3 and 4). Localized shimming was performed on the VOI using STEAM localization pulse sequence observing the proton signal. Localized shimming improved the linewith at half height about 12–15 and 30–40 Hz at the base. Image selected in vivo spectroscopy (ISIS) method was employed for volume-selective ^{31}P MRS [11]. Acquisition parameters were 4096 scans with 2.5 s repetition time, 4k data points and 2500 Hz sweep width. Phosphorous metabolites were calculated by computer integration of the areas under the respective peaks. Brain and cardiac energy status were evaluated by means of PCr/ATP ratio calculated by dividing PCr with β-ATP resonance area.

2.3. Echocardiography

Twenty female mice, 10 transgenic GFAP-bGH mice and 10 non-transgenic control mice were investigated. The animals were anesthetized with isoflurane (0.4–0.6%) and mixture of O_2 and N_2O 2:1, using a nose mask. The anterior chest was shaved and ECG leads

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