Neuregulins Response to Exercise: a Mini Review

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ABSTRACT

The Neuregulin is a member of the epidermal growth factors (EGF) family of receptor kinases, was originally identified as the product of the transforming gene derived from chemically induced rat neuroblasts. A variety of different protein isoforms are produced from single Neuregulin gene. Four distinct vertebrate gene encode Neuregulin, prosaically named NRG1, NRG2, NRG3, and NRG4. Most of biological function related to NRG1 which are widely acting on brain and nervous plasticity, cardiac muscle development and also as mediator skeletal muscle metabolism. The expression of NRGs mRNA in different tissues (brain, cardiac and skeletal muscles and adipose tissue) has been observed, but its expression in nervous system element, particularly in brain is well documented. A change in serum NRG1 has been observed in patient with schizophrenia and also considered as a biomarker of cardiovascular fitness. In addition, NRG1 injection has shown to improve glucose tolerance test, increased serum leptin, weight gain prevention, and reduce food intake in NRG1-treated minkes. The purpose of this short review paper was to see the responses of NRGs to different types of acute physical exercise or exercise training. In this regard, it seems exercise at different intensities should be a good candidate for future study in relation to NRGs response.

KEY WORDS: Neuregulin, NRG1, Exercise.

INTRODUCTION

Neuregulin or neuroregulins (NRGs) (also called NDF, heregulin, GGF and ARIA) is a member of the epidermal growth factor (EGF) family (1-3) The biological effects of the factor are mediated by tyrosine kinase receptors (ERB family) (4). Neuregulin can bind to mentioned receptor family members such as tyrosine-tyrosine kinase-B3 and -B4 (1, 5). In fact, neuregulin has four members: NRG1, NRG2, NRG3 and NRG4 and most of studies focused on the biological function of NRG1 and NRG2. Thus, less information is existed about NRG3 and NRG4 biological functions (6, 7). It has been suggested that neuregulins and their receptors play a crucial roles in nervous system and cardiac muscle, and breast development (6, 8-10). Neuregulins are mostly expressed in central nervous system and the first detected neuregulin gene called NRG1. In the brain, NRG1 contribute in synapse formation, activity-dependent synaptic plasticity, and acetylcholine receptor subunit expression (11). It has been reported that NRG1 play a neuroprotective role by promoting the glutamine-dependent neural cobalamin metabolism via stimulating cysteine uptake (12), control glutamate uptake by Up-regulating Excitatory Amino Acid Carrier 1 (EAAC1) (13), improves glucose tolerance in adult and old rats (14-16). Recently, a change in...
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muscle, and these changes are different between male and female rats (26).

In study by Lebrassuer et al. (2003) who investigated the acute effect of a change in NRG isoforms and its ErB2, ErB3 and ErB4 receptors were measured. Using immunofluorescence technique and analysis of muscle showed that mentioned receptors were localized clearly to the myocyte and ErB3 immunoreactivity was decreased in soleus compared to the EDL muscles. The expression of related receptors was accompanied with skeletal muscle NRG and the distribution was enriched but not confined to the neuromuscular junction. To investigate the effect of contractile activity on NRG processing in vivo, using intracellular and extracellular NRG antibodies showed that both forms of exercise resistance and endurance exercise (treadmill running) changed markedly the relative distribution of NRG in all muscle examined. They observed the disappearance of 183-kDa band and the concurrent increase in 64 and 48-kDa band in exercised vs control muscles (23).

In other study by Lebrassuer et al. (2005) effect of progressive resistance training on the expression on neuregulin and its receptors in human skeletal muscle was investigated. They reported that ErB2, 3, and 4 were abundant in human vastus lateralis muscle and NRG1. The results indicated that ErB3 was expressed in both fast and slow muscle fibers. In lebrassure et al. (2005) also indicated that no changes in the expression of ErB2 and ErB4 and the expression profiles of NRG1 were observed in 1 week and after 8 week of training program compared to baseline values. However, a significant increase in ErB3 (2.9 fold) at 1 week (2.9 fold) and at 8 weeks (2.5 folds) were observed. An increase in ErB3 not other ErB3 receptors was explained by authors. They mentioned that skeletal muscle ErbB and its upregulation in the absence of increased expression of other family members (ErB2 and ErB4) and ligand might be related to the content of PI3-K binding motifs (six binding motifs) in its C terminal and is therefore considered a primary mediator of NRG-dependent PI3-K activation. They also suggested that, in theory, increased ErbB3 expression may be a proximal event in response to exercise training to enhance activation of downstream targets of PI3-K associated with fiber hypertrophy (ie.. p70s6k and mTOR) an/or glucose uptake (ie.. protein kinase B/Akt and GSK3β) and its expression may in part contribute to exercise-related adaptation in trained muscle (24).

In study by Ennequin et al. (2015) who used investigated the effects of two interventions; diet and exercise training on skeletal muscle NRG1/ErbB signaling pathway. In this study high-fat /high sucrose (HF/HS) diets were employed for 16 weeks. The results indicated that diet induced obesity but did not result to a significant increase in NRG1 mRNA expression in skeletal muscle. However, using a western blot technique has revealed several bands mainly around 115-kDa, 70-kDa, and 42-kDa. These molecular sizes partially were similar to those reported previously by different researchers. The author mentioned that 115-kDa band corresponds to full length NRG1 and the 42 kDa to the cleaved active form of NRG1. In the other hand, NRG1 mRNA and protein levels did not changed in response to exercise training program. Furthermore, exercise or return to normal diet decreased full length NRG1 and increased cleaved NRG1 levels and NRG1 cleavage index was 1.5 fold. I rats in which return diet combined with exercise training a 3-fold increase in NRG1 cleavage was observed compared to the HF/HS group. It should be noted that ErbB4 and protein levels were significantly higher in trained groups. It seems under the study experimental conditions exercise training had a modest effect on the expression of different NRG1 variants. In this study a weight reduction was observed in HF/HS-exercise, normal-diet (ND), and ND-exercise groups not in H/HS-diet rats. In addition, NRG1 and protein levels did not revealed any change in response to exercise and normal diet. However, a reduction in full length NRG1 and increase in cleaved NRG1 levels and consequently also the NRG1 cleaved index approximately 1.5 fold and return to normal diet and exercise increased cleaved index to 3 folds in ND-E rats when compared to HF/HS treated rats. A higher EreB4 protein level and its phosphorylation ratio were observed only in trained groups not diet (15).

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On the basis of the present study results, authors hypothesized that endurance training might be more effective than resistance training to induce significant changes in NRG1 cleavage in skeletal muscle.

The effect of exercise training (16m/min, 50min, 5 days/week for 4 weeks) on NRG1/ErbB signal pathway in rat myocardial infarction model was investigated by Cai et al. (2016). They reported that analyzed data at infraction border zone of MI heart by immunohistochemical and western blot showed a slightly increase in NRG1 protein levels in Sed-MI group compared with the sham group. In addition, four weeks of endurance training resulted in a further increase in the NRG1 expression in comparison to the Sed-MI group. Endurance training also significantly increased the activation of ErbB2, ErbB4, PI3K and Akt. This in turn suggesting that endurance training activates NRG1/ErbB signaling. On the basis of the present study data, They suggested that four weeks of endurance training could produce a beneficial effect for heart regeneration. They also mentioned that it is not clear the increased levels of NRG1 is accumulative effect of prolonged endurance training or an acute response to single session of exercise (25).

In study by Waring et al. (2014) who examined the effects of low and high-intensities on NRG1 in Wistar rats. They reported that the greatest changes were observed on the levels of NRG1 following the high-intensity exercise and this change peaked at day 7 and still higher at day 14 than to baseline values during the exercise process. Author mentioned that NRG1 have been implicated in regulating cardiac hypertrophy and have also in myocyte replacement following cardiac injuries. Author suggested that a few weeks of vigorous exercise can significantly increase the myocyte count and mass indicates that this phenomena is an important component of cardiac physiology and homeostasis (27).

CONCLUSION

On the basis of reviewed studies, it seems that NRGs and its receptors are not expressed and functioned in nervous system particularly brain, but it also expressed in different tissues such as heart, skeletal muscle, adipose tissue, and means that NRGs isoforms paly different biological and developmental role in different tissues. It should be noted that the different biological and therapeutic roles of NRGs should not be taken less in attention because of its close relationship to nervous system and and NRGs significant changes in schizophrenic condition.

APPLICABLE REMARKS

- Thus, it would be logic and helpful to pay more attention on the benefits of exercise-induced NRGs at serum, protein and gene levels.

REFERENCES