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Review Article

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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 neuroblastoms. 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 mince. 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). Neuregulis 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 neuroprotctive 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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serum neuregulin in schizophrenia has been reported some authors how mentioned that NRG1 is implicated in the etiology or neuropathology of schizophrenia, although they also suggested that its biological contribution on this illness is not fully understood.(17, 18). Serum neuregulin-1β has reported to be used a markers in cardiovascular diseases (19). As mentioned above, serum neuregulin, particularly NRG1 is changing at different circumstance, specially in schizophrenia, diabetes, and might be in physical exercise as a metabolic and cardiovascular stressor (20-22). The effects of physical exercise and training on human and other species bodily function, especially on skeletal muscles, heart and brain is well known and documented. On the other hand, with consider to NRG1 roles in nervous system, cardiac muscle development and as a modulator of skeletal muscles function (22); very little information about the responses of NRGs and its isoforms to physical exercise/training (acute/chronic or by exercise modality) existed. Thus, the aim of this short paper is to review very less published article to determine the biological potential of NRG and open a window for future research.

MATERIALS AND METHODS

Subjects. The subjects of studies in this very short review article, authors employed (15, 23-27): The human (20 healthy males in age 19-21 yrs) subjects and rats (female and male Wistar and Sprague-Dawely) were employed in experimental design. In experiment with human subjects, the participants had not participation in any regular resistance or endurance exercise/training in previous.

Exercise Protocols. In Wang *et al*. (2014) study a 4 weeks resistance training program employed (26). Lebrassuer et al. (2003) recruited following protocols: single bout of an in vivo model of resistance exercise (RX) (Muscle contractions were produced in one hindlimb using a Grass S48 stimulator (Grass Instruments, Quincy, MA) at a frequency of 100 Hz to recruit both fast- and slow-twitch muscle fibers (6–12 V, 3-s duration, and 10-s delay, for 10 sets of 10 repetitions and 1-min recovery was given between sets, resulting in a protocol time of 45 min and also a single bout of treadmill running protocol (EX) for 45 min (23). The protocol consisted of 15 min at 21.7 m/min and a 15% incline and 15 min at 26.7 m/min and a 20% incline and concluded with 15 min at 31.7 m/min and a 25% incline, or until exhaustion, whichever came first. For the equivalent duration, control animals were placed on an adjacent treadmill, and the belt remained stationary (26). In second study on human subjects, Lebrassuer *et al*. (2005) used a progressive resistance training (80% 1RM, 3times/week, for 8 weeks, and 3 sets of 10 repetitions at 80% of their 1RM). Three Exercises; seated knee extension, recumbent leg press, and prone knee flexion were used. Strength was assessed every 2 weeks to maintain the training at 80% of the 1RM (24). Ennequin *et al.* (2015) in their study used combined diets and exercise program (15). Rat ran on a motorized treadmill at 0% degree started at 6 m/min^{-1} to 10 m/min^{-1} (55-60%VO_{2max}) and duration from 15 to 50 minutes, 5days/week, and for 8 weeks (15). Cai *et al*. (2016) was used an exercise training program at intensity of 16m/min,50min/session, 5days/week for 4 weeks (25). In this study, exercise training was started by 10m/min for 10minutes for first three days. The speeds and duration were gradually increased 50min/sessions. Waring *et al*. (2014) exercise protocols were endurance training on motorized treadmill for 30min/day, 4 days/week for up to 4 weeks at low (55–60% of individual $VO_{2\,max}$) or high (85–90% of $VO_{2\,max}$) intensities (27).

Variables measurement. Cardiac and skeletal muscle Neuregulin (NRG) isoforms and its ErbB receptors family by using different techniques were determined (15, 23-27).

RESULTS AND DISCUSSION

In Wang *et al*. (2014) study, they reported that rats underwent 4weeks resistance training resulted in up-regulated NRG1 protein expression of cardiac and skeletal muscle in male trained rats ,Erb B2 and Erb B4 expressions were both up-regulated in male and female rats. Author concluded that resistance training could promote cardiac function and skeletal muscle growth in female and male trained rats, increase NRG1 expression and its receptors in myocardial tissue and gastrocnemius

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 ErbB2, ErbB3 and ErbB4 receptors were measured. Using immunofluorescence technique and analysis of muscle showed that mentioned receptors were localized clearly to the myocyte and ErbB3 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 ErbB2, 3, and 4 were abundant in human vastus lateralis muscle and NRG1. The results indicated that ErbB3 was expressed in both fast and slow muscle fibers. In lebrassure *et al.* (2005) also indicated that no changes in the expression of ErbB2 and ErbB4 and the expression profiles of NRG1 were observed in 1week and after 8week of training program compared to baseline values. However, a significant increase in ErbB3 (2.9 fold) at 1 week (2.9 fold) and at 8 weeks (2.5 folds) were observed. An increase in ErbB3 not other ErbBs receptors was explained by authors. They mentioned that skeletal muscle ErbB and its upregulation in the absence of increased expression of other family members (ErbB2 and ErbB4) 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 NRG1mRNA 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 actyive 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 NRG1cleaved index approximately 1.5 fold and return to normal diet and exercise increased cleaved index to 3folds 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).

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 wetern 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 benficial effect for heart regeneration. They also mentioned that it is not clear the increased levels of NRG1 is acumulative 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 reoplacement 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 homoeostasis (27).

CONCLUSION

On the basis of reviewed studies, it seems that NRGs and its receptors are not expressed and functioned in nerous 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 schizophernic 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.

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