Fiscal Year:	FY 2006	**Task Last Updated:**	FY 01/08/2007
PI Name:	Reid, Michael B. Ph.D.		
Project Title:	Redox Modulation of Skeletal Muscle Function in Microgravity		
Division Name:	Human Research		
Program/Discipline:	NSBRI Teams		
Program/Discipline--Element/Subdiscipline:	NSBRI Teams--Muscle Alterations and Atrophy Team		
Joint Agency Name:		**TechPort:**	No
Human Research Program Elements:	(1) **HHC**:Human Health Countermeasures		
Human Research Program Risks:	(1) **Muscle**:Risk of Impaired Performance Due to Reduced Muscle Size, Strength and Endurance		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
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Zip Code:	40536-0298	**Congressional District:**	6
Comments:			
Project Type:	Ground	**Solicitation / Funding Source:**	NSBRI
Start Date:	09/01/2005	**End Date:**	08/31/2009
No. of Post Docs:	1	**No. of PhD Degrees:**	0
No. of PhD Candidates:	0	**No. of Master' Degrees:**	2
No. of Master's Candidates:	2	**No. of Bachelor's Degrees:**	1
No. of Bachelor's Candidates:	1	**Monitoring Center:**	NSBRI
Contact Monitor:		**Contact Phone:**	
Contact Email:			
Flight Program:			
Flight Assignment:			
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Jones, Jeffrey (NASA JSC) Kennedy, Ann (University of Pennsylvania) Sabet, Arman (University of Kentucky)		
Grant/Contract No.:	NCC 9-58-MA00701		
Performance Goal No.:			
Performance Goal Text:			
	NASA’s Critical Path Roadmap identifies loss of skeletal muscle function as a key concern for long-term missions. Gravitational unloading causes weakness of antigravity muscles due to loss of muscle mass (atrophy) and contractile dysfunction. In selected conditions, especially extravehicular activity (EVA), performance can also be limited by muscle fatigue. The current project evaluates selected compounds, nutritional supplements and pharmacologic agents, that may oppose oxidative stress in muscle and protect against weakness and fatigue. The experimental approach is designed to identify and develop countermeasures for human testing in the near-to-mid term. Initial experiments will define the loss of oxidant regulation that occurs with muscle unloading. Subsequent studies will evaluate compounds for protective effects on muscle function. The efficacy of each compound tested in this project is supported by preliminary data from animal studies, human trials, or both; each compound is approved for systemic administration to humans.		

Task Description:	Experiments will address three specific aims: Aim 1. To determine the time course, composition, and source of increased oxidant activity in unloaded muscle. Experiments will use mice conditioned by hindlimb unloading for up to two weeks. The antigravity muscle soleus will be studied to define the time course of oxidant dysregulation after unloading, to determine the relative contributions of reactive oxygen species vs. nitric oxide derivatives, and to test mitochondria as the primary source of increased oxidant activity. Aim 2. To evaluate selected antioxidants as countermeasures for weakness in unloaded muscle. In these experiments, mice conditioned by hindlimb unloading will be treated with one of four interventions that oppose oxidant activity or oxidant-mediated signaling: allopurinol (xanthine oxidase inhibitor), curcumin (NF-kappaB inhibitor), Bowman-Birk inhibitor complex (protease inhibitor), or N-acetylcysteine (NAC; reduced thiol donor). Unloaded soleus will be tested for protection against oxidative stress, contractile dysfunction, and muscle atrophy. Aim 3. To test NAC as a countermeasure for handgrip fatigue in humans. Experiments in healthy volunteers will define the appropriate preparation (solution vs. capsule) and dosage for oral NAC administration and will test NAC effects on handgrip strength and handgrip fatigue during concentric exercise.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	This research directly addresses two Earth-based problems, loss of function in unloaded muscle and muscle fatigue. The first problem occurs in individuals who are immobilized by injury or surgery. Muscles of the affected limbs atrophy and weaken, making it difficult for the individual to return to normal daily activity. The resulting inactivity lessens the quality of life, increases hospitalization and therapeutic costs, and increases the likelihood of pneumonia, venous thromboses, and other serious medical complications. A practical countermeasure to lessen atrophy and weakness would directly benefit these individuals, lessening the problems caused by transient immobilization. The second problem is familiar to us all. Acute muscle fatigue is a common feature of strenuous exercise. A countermeasure to inhibit fatigue would benefit a broad range of the US populace whose work requires physical exertion ranging from military professionals to firefighters, from police officers to construction workers. [The implications for professional athletes are all too obvious.]
Task Progress:	Our project is designed to address three sets of tasks, also known as specific aims. Our progress on each of these tasks is as follows: 1. To determine the time course, composition, and source of increased oxidant activity in unloaded muscle. Our experiments use mice conditioned by hindlimb unloading for up to three weeks. The antigravity muscle soleus is tested using functional and biochemical assays to determine any changes in free radical regulation by the muscle. Data from the previous year show that soleus muscles respond to hindlimb unloading by increasing the activity of NF-kappaB, a signaling molecule that promotes muscle atrophy. Also, soleus muscle mass decreases 43% after 10 days of unloading. This atrophy is biphasic, occurring rapidly over the first 3 days and then more slowly. Free radical activity in the muscle shows the opposite response, increasing during the first three days and then leveling off. These data suggest free radicals stimulate wasting of unloaded muscles. 2. To test selected antioxidants as possible countermeasures for weakness of unloaded muscle. Mice conditioned by hindlimb unloading are being treated with compounds that inhibit free radical activity. These include curcumin, N-acetylcysteine (NAC), allopurinol, and Bowman-Birk inhibitor concentrate (BBIC). Soleus muscle atrophy and contractile function are measured to determine the effectiveness of these possible countermeasures. We have found that antioxidant countermeasures vary in their effectiveness. Dietary supplementation with curcumin or NAC caused biochemical changes in the muscles that appeared promising. But the overall effects of these two compounds was unremarkable. Neither inhibited muscle atrophy or improved muscle function during unloading. In contrast, oral administration of allopurinol was protective. This compound lessened the weakness caused by muscle unloading despite the fact that muscle atrophy still occurred. 3. To evaluate NAC as a countermeasure for handgrip fatigue in humans. NAC has been shown to inhibit human muscle fatigue in several recent studies. Experiments in healthy volunteers are optimizing the preparation and dosage of oral NAC administration used to delay muscle fatigue during handgrip exercise. In the past year, we recruited a study coordinator and created a specially-designed device (‘ergometer’) to measure handgrip fatigue. The new ergometer overcomes several limitations of an earlier machine used in our previous research studies. We hope the new ergometer will provide more reliable measurements. We are now conducting dose-response studies of NAC capsules administered orally. To date we have screened 11 volunteers. Eight were unable to perform our fatiguing exercise protocol reproducibily and have been excused from the study. Three individuals have successfully completed the entire protocol and their blood samples are currently being analyzed to determine NAC effects.
Bibliography Type:	Description: (Last Updated: 08/24/2020)
Articles in Peer-reviewed Journals	Matuszczak Y, Farid M, Jones J, Lansdowne S, Smith MA, Taylor AA, Reid MB. "Effects of N-acetylcysteine on glutathione oxidation and fatigue during handgrip exercise." Muscle Nerve. 2005 Nov;32(5):633-8. PMID: 16025522 , Nov-2005
Articles in Peer-reviewed Journals	Reid MB. "Response of the ubiquitin-proteasome pathway to changes in muscle activity." Am J Physiol Regul Integr Comp Physiol. 2005 Jun;288(6):R1423-31. Review. PMID: 15886351 , Jun-2005
Articles in Peer-reviewed Journals	Smith MA, Reid MB. "Redox modulation of contractile function in respiratory and limb skeletal muscle." Respir Physiol Neurobiol. 2006 Apr 28;151(2-3):229-41. Epub 2006 Feb 14. Review. PMID: 16481226 , Apr-2006
Awards	Reid MB. "Citation for Distinguished Service, American Physiological Society (MB Reid)." Jan-2006
Awards	Reid MB. "Distinguished Service Award, College of Health Sciences, University of Kentucky (MB Reid)." Jan-2006
Awards	Reid MB. "Mentor Recognition Award, Clinical and Translational Science Conference, University of Kentucky (MB Reid)." Jan-2006