

Effect of Unrestricted Access to Running Wheels on Cancer-Related Fatigue

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### **Abstract**

Cancer-related fatigue (CRF) occurs in 60-90% of cancer patients and significantly reduces functional status. Tumor growth causes significant wasting of skeletal muscle, thought to be a major factor in CRF. Cancer patients also report depressed mood, contributing to feelings of fatigue. Exercise has been shown to have anti-depressant effects in mice and humans, though its effect on tumor-induced muscle wasting has not been studied. The purpose of the study is to determine the effect of voluntary wheel running activity (VWRA) on muscle mass and depression-like behavior in a mouse model of CRF. In mice, fatigue is modeled as a decline in VWRA and depression is modeled as anhedonia, a loss of preference for sucrose solution. Twenty adult female, age-matched mice were divided into 4 groups, half having ad libitum access to running wheels and half serving as sedentary controls. Half of each group was inoculated with tumor cells and half were healthy controls. VWRA, sucrose preference and total fluid intake were measured on days 1, 7, 14, and 19 of tumor growth. Mice were euthanized on day 21 and the gastrocnemius muscle and spleen were weighed. Unrestricted access to exercise wheels did not affect sucrose preference compared with sedentary animals, and there was no evidence of anhedonia in tumor-bearing mice. Unrestricted access to exercise wheels did not improve muscle mass though VWRA was significantly correlated with muscle mass. Further studies are needed to determine if exercise improves muscle mass, fatigue, and depression in cancer patients.

## Statement of the Problem

### Introduction

Fatigue and depression are two symptoms frequently associated with cancer. They can be present during and after cancer treatment for a wide range of tumor types. Cancer related fatigue (CRF) is characterized by an excessive sense of tiredness, unaffected by rest or sleep, that interferes with daily functioning and quality of life. CRF often co-occurs with depression, but can be found in isolation (Minton, Richardson, Sharpe, Hotopf, & Stone, 2008).

### Background

Cancer-related fatigue (CRF) is a condition characterized by extreme tiredness, weakness, and lack of energy (Hofman, Ryan, Figueroa-Moseley, Jean-Pierre, & Morrow, 2007). Depression is also often associated with CRF (Cella, Davis, Breitbart, & Curt, 2001) This symptom cluster can afflict cancer patients at all stages of the disease process, from treatment to survivorship (Ryan et al., 2007). Moreover, CRF can last from months to years following completion of treatment, and is the most distressing symptom reported by cancer survivors (Hofman, et al., 2007). Prevalence of CRF has been reported between 60 and 90% and is a significant cause of morbidity (Cella, et al., 2001). The prevalence of CRF is on the rise as the use of more aggressive therapies and cancer survivorship also rises. During treatment, CRF can cause a delay in chemotherapy administration, impede adherence to treatment regimens, or affect the dose of chemotherapy that can be given due to the severity of fatigue experienced by the patient (Hofman, et al., 2007).

The underlying mechanisms of CRF are poorly understood, which makes it even more difficult to discern the cause. Proinflammatory cytokines, namely interleukin-1beta (IL-1 $\beta$ ),

interleukin-6 (IL-6), and TNF- $\alpha$  have been implicated in the development of skeletal muscle wasting and depressed mood, both of which are thought to contribute to CRF. Pro-inflammatory cytokines are produced either by the tumor or as a host response to tumor growth. In muscle, cytokines activate mechanisms causing hypoanabolism and hypercatabolism, which causes muscle wasting or loss of lean body mass. Furthermore, TNF- $\alpha$  and IL-6, are thought to contribute to weight loss and skeletal muscle wasting, also called cachexia, in persons with advanced cancer (Wang, 2008).

There is also increasing evidence linking chronic inflammation and pro-inflammatory cytokines with depression (Capuron et al., 2002). In animal models, administration of the endotoxin, lipopolysaccharide (LPS), has been shown to increase cytokine production and induce “sickness behavior,” which includes anhedonia, the inability to experience pleasure, and reduced physical activity. The presence of these cytokines leads to alterations in the production of serotonin and serotonin transporters in brain areas important in the regulation of mood and activity (Miller, Ancoli-Israel, Bower, Capuron, & Irwin, 2008). In rodents, anhedonia is modeled as decreased preference for sweetened water or milk.

Clinicians are in agreement that depressed mood is often present in patients with CRF, though it is not known if treatment of depression would reduce the severity of fatigue. Conversely, lack of energy and reduced physical activity are a significant component of depression. The resulting decline in physical activity could contribute to loss of muscle mass over time.

## **Purpose**

The purpose of this study is to determine if physical activity, modeled as unrestricted access to running wheels, will affect mood and muscle mass in tumor-bearing mice. In mice, depressed mood is modeled as a reduced preference for sucrose solution. Fatigue is modeled as a decrease in voluntary wheel running activity (VWRA). We expect to observe:

1. Increased sucrose preference in tumor-bearing mice that have unrestricted access to running wheels when compared to sedentary mice.
2. Increased VWRA in tumor-bearing mice that have unrestricted access to running wheels when compared to sedentary mice
3. Increased muscle mass in mice with unrestricted access to running wheels compared to sedentary controls.

## **Significance**

CRF is a debilitating experience for cancer patients. As fatigue has no one defined etiology and no targeted treatments, it often is unrecognized and undertreated. CRF can significantly impact the financial and social burden of cancer treatment and management. If exercise can improve mood and reduce skeletal muscle wasting, it may be effective in reducing CRF.

## **Review of Literature**

CRF is defined as overwhelming tiredness, weakness, and lack of energy. These symptoms can significantly reduce quality of life, impair functional status, alter social roles, and cause significant financial burden. CRF is composed of both a central component and a

peripheral component. Centrally, fatigue is the result of changes in the hypothalamic-pituitary-adrenal (HPA) axis and neuronal systems controlling arousal and activity. Peripherally, fatigue is the result of alterations in skeletal muscle function (Narayanan & Koshy, 2009).

A significant component of peripheral fatigue in cancer patients is skeletal muscle wasting. Skeletal muscle wasting is the result of an imbalance between protein synthesis and protein catabolism. The inflammatory response to tumor growth stimulates protein degradation pathways which lead to protein catabolism and loss of skeletal muscle mass. Muscle function is proportional to muscle mass in both humans and mice (Weber et al., 2009; Gorselink et al., 2006). A study by Diffie, et al. (2002) demonstrated that tumor-bearing mice had changes in myosin heavy chain type I and II proteins in the soleus muscle which would affect objective muscle function and resistance to fatigue.

CRF often co-occurs with depressed mood, which reduces motivation to engage in physical activity. The subsequent decrease in physical activity could contribute to additional loss of muscle mass, further reducing skeletal muscle function. Fatigue is often worse in patients that also experience depressed mood (Kuhnt et al., 2009). Animal models have been used to demonstrate that acute and chronic activation of the immune system leads to “sickness behavior,” characterized by lethargy and depressed mood. While lethargy resolves spontaneously after a few days of immune activation, depressive symptoms such as anhedonia persist (Moreau et al., 2008). In one study, animals exhibiting sickness behavior after LPS administration showed no anhedonia when given the tricyclic antidepressant imipramine (Dunn, Swiergiel, & de Beaurepaire, 2005). Furthermore, the symptoms of “sickness behavior” closely mirror depressive behaviors exhibited by cancer patients. Thus, measuring anhedonia can be an effective method to differentiate between fatigue and depressive behaviors.

Studies using animal models have clearly shown that proinflammatory cytokines such as IL-1 $\beta$ , IL-6, and TNF- $\alpha$  are involved in the onset of sickness behaviors (De La Garza, 2005). Depressive behaviors have been linked with increased expression of pro-inflammatory cytokines in the brain, as well as 2,3-indolamine oxygenase (IDO) (O'Connor et al., 2009). IDO is a competitive antagonist to serotonin synthesis, and reduces the conversion of tryptophan to serotonin. Serotonin is a neurotransmitter implicated in both mood regulation and locomotor activity. Pro-inflammatory cytokines also reduce serotonin activity in the brain by increasing the activity of serotonin transport proteins (Zhu, Blakely, & Hewlett, 2006; Su et al., 2009; Muller & Schwartz, 2007; Harden, du Plessis, Poole, & Laburn, 2006). However, drugs that increase serotonin activity in the brain, such as selective serotonin re-uptake inhibitors, do not reduce fatigue in cancer patients (Minton, et al., 2008; Breitbart & Alici, 2008).

In muscle, IL-1 $\beta$ , IL-6, and TNF- $\alpha$  activate the signaling pathways implicated in myosin degradation. TNF- $\alpha$  activates NF- $\kappa$ B, which increases muscle expression of MAFbx and MuRF1, two E3 ligases in the ubiquitin-proteasome pathway of myosin protein degradation (Acharyya & Guttridge, 2007; Acharyya et al., 2004). TNF- $\alpha$  also increases expression of Bnip3, which is implicated in the lysosome-mediated autophagy of cell organelles (Saini, Faulkner, Al-Shanti & Stewart, 2009; Zhao, Brault, Schild, & Goldberg, 2008). Proteolysis Inducing Factor (PIF) has been shown to come directly from the tumor cells, and also to contribute to decreased protein synthesis and protein degradation in skeletal muscle (Tisdale, 2004). While these findings implicate TNF- $\alpha$  in skeletal muscle wasting in cancer patients, agents that block TNF- $\alpha$  activity have not demonstrated effectiveness at maintaining lean body mass or reducing fatigue in patients with cancer cachexia (Jatoi et al., 2009).

TNF- $\alpha$  also increases expression of COX-2 through activation of NF- $\kappa$ B, which has been associated with increased skeletal muscle wasting. Non-steroidal anti-inflammatory drugs (NSAIDs), which inhibit both COX-1 and COX-2, have been shown to reduce muscle wasting and expression of MAFbx, MuRF1, and type 1 TNF- $\alpha$  receptor in tumor-bearing mice (Graves, Ramsay & McCarthy, 2006; Hitt, Graves & McCarthy, 2005). Another study showed that COX inhibition reduced depressive behaviors in mice injected with lipopolysaccharide (LPS) without reducing expression of pro-inflammatory cytokines in the brain (Teeling, Cunningham, Newman & Perry, 2010; Teeling et al., 2007). More research is needed to better understand the contribution of COX to sickness symptoms associated with increased cytokine activity.

There is mounting evidence demonstrating that aerobic exercise has both antidepressant and anti-inflammatory qualities. Skeletal muscle produces IL-6 during exercise, which can reduce IL-1 $\beta$  and TNF- $\alpha$  (Wood, Nail, & Winters, 2009). Chronic exercise has been shown to improve depressive behaviors in rats exposed to uncontrollable stress (Greenwood et al., 2003). Duman, Schlesinger, Russell & Duman (2008) demonstrated that mice with free access to running wheels showed decreased depression-like behaviors in the forced swim test and the tail suspension test. Hoffman-Goetz, Pervaiz, Packer, & Guan (2010) found that healthy mice with free access to running wheels showed a reduction in intestinal lymphocyte TNF- $\alpha$ , and an overall increase in serum levels of IL-10 and IL-6 compared to sedentary mice.

Aerobic exercise has also been shown to improve cognitive function and reduce depressive symptoms in animals and humans (Churchill et al., 2002; Daley et al., 2007; Segar et al., 1998). Similarly, several studies have shown that exercise improves quality of life during cancer treatment and reduces the subjective experience of fatigue (Velthuis, Agasi-Idenberg, Aufdenkampe, & Wittink, 2009; Wood, et al., 2009; Spence, Heesch, & Brown, 2010).

## **Method**

### **Introduction**

The study employed a quantitative experimental design with random assignment to conditions (tumor, wheels). Tumor growth was induced using the Lewis Lung carcinoma cell line. The tumor cells were injected between the scapulae to reduce the likelihood that tumor growth would affect mobility. In the LLC model of tumor-induced muscle wasting, progressive tumor growth does not suppress food or fluid intake until the mice become moribund, typically between 21 to 24 days of tumor growth. The study tested the hypothesis that unrestricted access to running wheels will improve VWRA, sucrose preference and skeletal muscle mass in tumor-bearing mice. The research subjects were 20 age-matched C57Bl/6 female mice. Female mice were chosen for this study because female mice run more than male mice. The subjects were placed into four groups: no tumor/no wheels, tumor/no wheels, tumor/wheels, no tumor/wheels. All procedures were approved by the Institutional Animal Care and Use Committee.

### **Voluntary Wheel Running Activity**

Healthy mice normally run on wheels for 2-3 miles a night, and demonstrate reduced VWRA as a result of acute or chronic activation of the immune or inflammatory response, or tumor growth. (Skinner, et al., 2009; Wood, et al., 2006). With tumor growth, mice run for shorter periods of time with increasing time between running episodes, resulting in reduced overall wheel revolutions. In the present study, VWRA was measured over 18 hours, including the nocturnal phase of activity at baseline (day 0) and on days 7, 14, and 19 of tumor growth. Running was measured using the Columbus Instruments Mouse Home Cage Running Wheels shown in Figure 1. Each wheel had a magnetic indicator connected to a wheel counter which is

connected to a personal computer. Software provided by Columbus Instruments was used to define intervals and time frames to measure VWRA. The magnetic sensor counted each wheel turn which was then stored cumulatively in the computer software by interval. Wheels were suspended in the cages under the wire food and water holder.

Figure 1.



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### **Sucrose Preference Test**

In rodents, depressed mood is modeled as anhedonia, reduced interest in pleasurable activity, measured as a reduced intake of palatable substances, such as sucrose pellets or sweetened milk (Yirmiya, 1996). Ideally, animals with access to both nutritive substances, such as food and water, and palatable substances will choose the palatable substance even when nutrition and fluid requirements are already met (De La Garza, 2005). Sucrose preference was used to measure anhedonia and was tested at baseline (day 0), and on days 7, 14, and 19 of tumor growth.

On the day of testing, water bottles were replaced with two 50mL tubes, one containing water obtained from the animal care facility, and one containing 3% sucrose solution. Sucrose intake and water intake were measured the following morning. Each bottle was weighed before and after the test period and sucrose preference was calculated using the following formula:

$$SP = \frac{\text{sucrose solution intake (g)} \times 100}{\text{total fluid intake (g)}}$$

## Procedure

All mice were housed individually, and acclimated to the cage environment and presence of running wheels for 1 week. Mice that did not demonstrate a stable pattern of nocturnal running were removed from the experiment. On day 0 of the experiment, baseline VWRA, food intake, total fluid intake, and intake of sucrose solution were measured. Upon completion of baseline testing, running wheels were removed from the sedentary (no wheels) group of mice.

Half of the mice in the sedentary and running groups were injected between the scapulae with 0.2mL saline containing  $5 \times 10^5$  Lewis Lung Carcinoma (LLC) cells obtained from American Type Tissue Culture (Manassas, VA, USA) and half were injected with 0.2mL of normal saline solution. Animals that did not have palpable tumors by day 9 were removed from the experiment. VWRA, sucrose preference, and food and fluid intake were measured on days 7, 14, and 19. On the day of testing, wheels were placed in the cages of sedentary mice. Water bottles were replaced with two 50mL tubes with rubber stoppers and sippers. One tube contained normal animal care facility water, and one contained 3% sucrose solution. SP and VWRA were measured from 4pm to 10am. Mice were euthanized on day 21 of tumor growth followed by cervical dislocation. The gastrocnemius muscle and spleen were removed, wrapped in foil, flash-

frozen in liquid nitrogen and stored at  $-80^{\circ}\text{C}$ . To account for variations in body size between subjects, gastrocnemius muscle mass was determined by calculating the average of the right and left gastrocnemius muscle and dividing by body weight. VWRA is reported as mean wheel count per day. To account for differences in VWRA for any given mouse, mean change in VWRA between baseline and day 7, day 7 and day 14, and day 14 and day 19 was also determined.

### **Data Analysis**

The independent variables were tumor and unrestricted access to running wheels. The dependent variables were muscle mass, VWRA, change in VWRA, and SP. Data were first analyzed for means and standard deviations among the 4 groups. A two-way (tumor, wheels) analysis of variance (ANOVA) was used to test effects of the independent variable on each dependent variable. Bivariate correlations were used to examine relationships between dependent variables. A probability of less than .05 was considered statistically significant.

### **Results**

Tumor growth had a significant effect on relative gastrocnemius muscle mass ( $p < .001$ ), but there was no effect of unrestricted access to running wheels on muscle mass. Spleen size was significantly greater in the tumor-bearing mice compared to non-tumor-bearing mice ( $p = .029$ ), confirming the presence of a systemic inflammatory response in tumor-bearing mice, but was not affected by access to running wheels ( $p = .955$ ). Mean spleen weight, muscle mass and VWRA of day 19 for each of the 4 groups is shown in Table 1. Neither tumor growth nor unrestricted access to running wheels had an effect on VWRA measured on days 7, 14, or 19. However, when VWRA was evaluated in terms of net change, a significant decrease occurred between day 14 and 19 in the tumor group ( $p = .004$ ), but not in the treatment group.

Relative mass of the gastrocnemius muscle was inversely correlated with spleen mass ( $r=-.717$ ,  $p=.001$ ) indicating that inflammation has a negative effect on muscle mass. Spleen mass was also negatively correlated with running on day 19 of tumor growth ( $r=-.537$ ;  $p=.018$ ). There was no correlation between VWRA on day 19 and muscle mass.

There were no tumor or treatment effects on sucrose preference (SP). Furthermore, SP on day 19 was not correlated with spleen weight or muscle mass. Similarly, no significant correlations were observed between SP on any test day and spleen weight or muscle mass. Correlations are shown in Table 2.

Table 1.

*Means and Standard Deviations*

Group	n	Gastrocnemius Mass (mg/g) (SD)	Spleen Weight (g) (SD)	Tot. Wheel Running 19 (SD)
Tumor	6	4.97 (0.58)	369.50 (217.29)	1568.67 (1952.07)
Tumor+Treatment	6	5.03 (0.35)	232.83 (98.29)	1048.40 (1216.43)
Control	4	6.10 (0.19)	102.25 (11.11)	1172.75 (850.14)
Control+Treatment	3	5.81 (0.11)	93.00 (9.85)	2895.50 (2423.85)

Table 2.

*Correlations*

Group	Rel. Gastr	Spleen	VWRA19	SP19
Rel. Gastr	1	-.717*	.432	-.170
Spleen		1	-.537*	.074
VWRA19			1	-.393
SP19				1

\* Statistically significant ( $p < .05$ )

### **Summary, Conclusions, Findings**

In summary, the study confirmed that tumor growth causes a systemic inflammatory response, as demonstrated by greater spleen mass size in tumor vs. control groups. The study found tumor growth also causes a significant reduction in skeletal muscle mass when compared to healthy controls. Tumor growth also caused a significant decrease in VWRA from day 14 to day 19, supporting wheel running as a model for CRF. The study did not demonstrate that unrestricted access to running wheels affected muscle mass, VWRA, a measure of fatigue, or SP, a measure of anhedonia.

### **Discussion**

In the present study, growth of the LLC tumor in mice caused a systemic inflammatory response, indicated by an enlarged spleen in the tumor-bearing mice. Tumor growth also caused a significant reduction in muscle mass and VWRA in the tumor-bearing mice compared to age-matched healthy controls. However, we did not observe an effect of tumor growth on sucrose preference at any time point tested.

Unrestricted access to running wheels did not affect muscle mass, VWRA or SP in tumor-bearing or healthy control mice. However, an effect may not have been detected due to the small sample size of only 12 tumor-bearing mice and 7 healthy controls. Furthermore, SP testing was concurrent with testing of VWRA. In mice, running has antidepressive effects, and thus measuring VWRA and SP simultaneously could confound SP. Another consideration is that SP was tested using a 3% sucrose solution. Since C57 mice are sensitive to sweet taste, this concentration may be too high (Sclafani, 2005).

There was a very wide variation in wheel counts among all groups. While the study was able to demonstrate a relationship between decline in VWRA and tumor growth by comparing the change in running between days 14 and 19, there was no relationship between mice with unrestricted access to running wheels and healthy controls.

In summary, Hypothesis 1 was not confirmed as the present study was unable to demonstrate a difference in sucrose preference between tumor-bearing mice and healthy controls. Moreover, there was no difference in sucrose preference between sedentary mice and mice with unrestricted access to running wheels. Hypothesis 2 was not confirmed as there was no difference in VWRA between sedentary mice and those with unrestricted access to wheels. Hypothesis 3 was not confirmed because there was no significant difference of muscle mass between the sedentary mice and those with unrestricted access to running wheels. More studies are needed to determine if aerobic activity will preserve muscle mass, reduce fatigue and improve mood in patients with cancer-related fatigue.

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