Reviewer's report

Title: Voluntary Exercise Inhibits Intestinal Tumorigenesis in Azoxymethane/Dextran Sulfate Sodium-Treated and ApcMin/+ Mice

Version: 1 Date: 19 March 2008

Reviewer: Jan Erik Paulsen

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Major Compulsory Revisions

Ju et al. present interesting results indicating that voluntary exercise may inhibit intestinal tumorigenesis in AOM/DSS-treated mice and Apc Min/+ mice, and that the inhibitory effect may be associated with decreased IGF-1/IGFBP-3 ratio, aberrant β-catenin signalling as well as arachidonic acid metabolism. However, the lack of symmetry in the study design is somewhat confusing, and it disturbs the presentation and interpretation of results. Examples: in the AOM/DSS study only males were used, and in the Apc Min/+ study only females were used; the high-fat diet given to CF-1 mice treated with AOM/DSS was AIN93M modified with a mixture of fats (20%) whereas as the high-fat given to Apc Min/+ mice was AIN-76 containing 20% of unspecified fats (was it corn oil?); in the Apc Min/+ mice studies, AIN93G was the basis for the low-fat diet (experiment 1) and AIN76A was the basis for the high-fat diet (experiment 2); in experiment 1 the small intestine was divided into 2 regions and no tumor size categories were presented (the size of the tumors was not scored), in experiment 2 the small intestine was divided into 3 regions and 3 tumor size categories were presented; no data on mechanisms were given in the AOM/DSS study; data on IGF and IGFBP-3 is only given for experiment 2; whereas the tumor levels of PGE2 and LTB4 are given in both experiment 1 and 2, the serum levels are only given in experiment 2.

Altogether I think this paper will be improved if the presentation is concentrated on data from the Apc Min/+ mice, and if the results are presented as two separate/different experiments. The AOM/DSS study could be presented in a separate paper including more tumor data and additional information about on the levels of IGF, PGE2 etc.

Specific comments:
1 The rationale for analysing IGF, IGFBP-3, PGE2 and LTB4 should be presented in the Introduction
2 Table I. The tumor incidence is low; why did you not search for microadenomas and smaller dysplasias? When you have length, width and height of the tumor it is possible to calculate the volume by the formula #/6*l*w*h. Why did you use one-tailed t-test?
3 The changes observed in body weight and fat compartments should in general
be presented in the tables, not only in the text. In the Apc Min/+ mice, voluntary 
exercise led to reduced fat storage, but the final bodyweight was not changes; 
what compensated for this loss, was it increased skeleton muscles weight?

4 There is little information on energy balance. There was a slight increase in 
dietary intake in experiment 1 (low-fat) in the exercise group. Was it observed 
such a difference in the high-fat experiment? Information about differences in 
energy intakes could help to estimate the energy used in the wheel-running 
activity.

5 When tumor #-catein and E-cadherin levels were compared between the 
experimental groups, were the tumors selected from the same size group? It is 
important to control for this because the levels of these proteins may vary with 
tumor size.

6 That exercise seems more effective on large tumors than small tumors may 
simply mean that the effect is due to a growth inhibitory effect. Have you 
compared the tumor size between the groups?

7 In the discussion new results from a couple of regression analyses were 
presented. These should be presented in the Results section, even if they were 
negative and seemed less important.

What next?: Unable to decide on acceptance or rejection until the authors have 
responded to the major compulsory revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a 
statistician.

Declaration of competing interests:

I declare that I have no competing interests