C60 FULLERENE EFFECT ON THE DYNAMICS OF FATIGUE PROCESSES IN RAT SOLEUS MUSCLE AFTER ISCHEMIA-REPERFUSION

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Effect of pristine C$_{60}$ fullerene aqueous colloid solution (C$_{60}$FAS; 1 mg/kg dose) on the dynamics of fatigue processes in rat soleus muscle after ischemia-reperfusion injury using the tensiometric method was studied. Experiments were conducted during the first 5 h and for 5 days after ischemia. The changes in maximal strength of muscle contraction and its level of generation between the beginning and end of stimulated irritation after intravenous and intramuscular administration of C$_{60}$FAS unmodified fullerene aqueous colloid solution were analyzed. The pronounced protective effect of this drug on the dynamics of skeletal muscle contraction was first determined. Protective effect of C$_{60}$FAS unmodified fullerene aqueous colloid solution relative to changes in the levels of muscle contraction strength generation between the beginning and end of stimulated irritation was 15% in the first 5 h after ischemia and increased to 92% on the 5th day of the experiment. In such a case, the intravenous therapeutic administration of C$_{60}$ fullerene aqueous colloid solution was the most optimal: the protective effect was 67% versus 49% under intramuscular administration. Thus, the development of biomedical nanotechnology with the application of pristine C$_{60}$ fullerene as a strong antioxidant opens up new possibilities in prevention and treatment of ischemic injury in the skeletal muscles.

**Key words:** C$_{60}$ fullerene, skeletal muscle contraction, ischemia-reperfusion injury.

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REFERENCES

1. Medicinal chemistry and pharmacological potential of fullerenes and carbon nanotubes. Series: Carbon materials: chemistry and physics. Cataldo F., Da Ros T. (eds.). V. 1, Springer
2. Zhu J., Ji Zh., Wang J., Sun R., Zhang X., Gao Y., Sun H., Liu Y., Wang Z., Li A., Ma J., 
Wang T., Jia G., Gu Y.  Tumor-inhibitory effect and immunomodulatory activity of fullerol 
C60(OH)x.  Small. 2008, V. 4, P. 1168–1175.

3. Prylutska S. V., Burlaka A. P., Klymenko P. P., Grynyuk I. I., Prylutskyy Yu. I., Schuetze Ch., 
Ritter U.  Using water-soluble C60 fullerenes in anticancer therapy.  Cancer Nanotechnol. 
2011, V. 2, P. 105–110.  
http://dx.doi.org/10.1007/s12645-011-0020-x

4. Prylutska S. V., Burlaka A. P., Prylutskyy Yu. I., Ritter U., Scharff P.  Pristine C60 fullerenes 
hinhibit the rate of tumor growth and metastasis.  
Exp. Oncol.  
2011, V. 33, P. 162–164.

5. Mchedlov-Petrossyan N. O.  Fullerenes in liquid media: an unsettling intrusion into the 
solution chemistry.  Chem. Rev. 2013, V. 113, P. 5149–5193.  
http://dx.doi.org/10.1021/cr3005026

6. Hirsch A., Brettreich M.  Fullerenes — chemistry and reactions.  New York: John Wiley & 
Sons , 2005.

7. Prilutski Yu., Durov S., Bulavin L., Pogorelov V., Astashkin Yu., Yashchuk V., Ogul'chansky 
T., Buzaneva E., Andrievsky G .  Study of structure of colloidal particles of fullerenes in water 
solution.  Mol. Cryst. Liq. Cryst. 1998, V. 324, P. 65–70.  
http://dx.doi.org/10.1080/10587259808047135

8. Prylutskyy Yu. I., Durov S. S., Bulavin L. A., Adamenko I. I., Moroz K. O., Geru I. I., Dihor I. 
N., Scharff P., Eklund P. C., Grigorian L.  Structure and thermophysical properties of 
fullerene C60 aqueous solutions.  Int. J.
9. Prylutskyy Yu. I., Buchelnikov A. S., Voronin D. P., Kostjukov V. V., Ritter U., Parkinson J. A., Evstigneev M. P. C60 fullerene aggregation in aqueous solution. Phys. Chem. Chem. Phys. 2013, V. 15, P. 9351–9360. 
http://dx.doi.org/10.1039/c3cp50187f

10. Prylutska S., Bilyy R., Overchuk M., Bychko A., Andreichenko K., Stoika R., Rybalchenko V., Prylutskyy Y., Tsierkezos N. G., Ritter U. Water-soluble pristine fullerenes C60 increase the specific conductivity and capacity of lipid model membrane and form the channels in cellular plasma membrane. J. Biomed. Nanotechnol. 2012, V. 8, P. 522–527. 
http://dx.doi.org/10.1166/jbn.2012.1404

11. Johnston H. J., Hutchison G. R., Christensen F. M., Aschberger K., Stone V. The biological mechanisms and physicochemical characteristics responsible for driving fullerene toxicity. Toxicol. Sci. 2010, V. 114, P. 162–182. 
http://dx.doi.org/10.1093/toxsci/kfp265

12. Prylutska S. V., Matyshevskaya O. P., Golub A. A., Prylutskyy Yu. I., Potebnya G. P., Ritter U., Scharff P. Study of C60 fullerenes and C60-containing composites cytotoxicity in vitro. Mater. Sci. Engineer. C: Mater. Biolog. Appl. 2007, V. 27, P. 1121–1124.

13. Prylutska S. V., Grynyuk I. I., Grebinyk S. M., Matyshevskaya O. P., Prylutskyy Yu. I., Ritter U., Siegmund C., Scharff P. Comparative study of biological action of fullerenes C60 and carbon nanotubes in thymus cells. Mat.-wiss. Werkstofftech. 2009, V. 40, P. 238–241.
14. Krustic P. J., Wasserman E., Keizer P. N., Morton J. R., Preston K. F. Radical reactions of C60. Science. 1991, V. 254, P. 1183–1185.

15. Scharff P., Carta-Abelmann L., Siegmund C., Matyshevska O. P., Prylutska S. V., Koval T. V., Golub A. A., Yashchuk V. M., Kushnir K. M., Prylutskyy Yu. I. Effect of X-ray and UV irradiation of the C60 fullerene aqueous solution on biological samples. Carbon. 2004, V. 42, P. 1199–1201. http://dx.doi.org/10.1016/j.carbon.2003.12.055

16. Gharbi N., Pressac M., Hadchouel M., Szwarc H., Wilson S.R., Moussa F. C60 fullerene is a powerful antioxidant in vivo with no acute or subacute toxicity. Nano Lett. 2005, V. 5, P. http://dx.doi.org/10.1021/nl051866b 2578–2585.

17. Prylutska S. V., Grynyuk I. I., Matyshevska O. P., Prylutskyy Yu. I., Ritter U., Scharff P. Anti-oxidant properties of C60 fullerenes in vitro. Fullerenes, Nanotubes, Carbon Nanostruct. 2008, V. 16, P. 698–705. http://dx.doi.org/10.1080/15363830802317148

18. Lai Y. L., Murugan P., Hwang K.C. Fullerene derivative attenuates ischemia-reperfusion induced lung injury. Life Sci. 2003, V. 72, P. 1271–1278. http://dx.doi.org/10.1016/S0024-3205(02)02374-3

19. Lai H. S., Chen W. J., Chiang L. Y. Free radical scavenging activity of fullerenol on the ischemia-reperfusion intestine in dogs. World J. Surg. 2000, V. 24, P. 450–454. http://dx.doi.org/10.1007/s002689910071
20. Yang D. Y., Wang M. F., Chen I. L., Chan Y. C., Lee M. S., Cheng F. C. Systemic administration of water-soluble hexasulfonated C60 (FC(4)S) reduces cerebral ischemia induced infarct volume in gerbils. *Neurosci. Lett.* 2001, V. 311, P. 121–124. [http://dx.doi.org/10.1016/S0304-3940(01)02153-X](http://dx.doi.org/10.1016/S0304-3940(01)02153-X)

21. Lin A. M. Y., Fang S. F., Lin S. Z., Chou C. K., Luh T. Y., Ho L. T. Local carboxyfullerene protects cortical infarction in rat brain. *Neurosci. Res.* 2002, V. 43, P. 317–321. [http://dx.doi.org/10.1016/S0168-0102(02)00056-1](http://dx.doi.org/10.1016/S0168-0102(02)00056-1)

22. Andreichenko K. S., Prylutskaya S. V., Medyńska K. O., Bogutska K. I., Nurishchenko N. E., Prylutskyy Yu. I., Ritter U., Scharff P. Effect of fullerene C60 on ATPase activity and superprecipitation of skeletal muscle acto-myosin. *Ukr. Biokhim. Zh.* 2013, V. 85, P. 20–26.

23. Prylutskyy Yu. I., Petrenko V. I., Ivankov O. I., Kyzyma O. A., Bulavin L. A., Litsis O. O., Evstigneev M. P., Cherepanov V. V., Naumo-vets A. G., Ritter U. On the origin of C60fullerene solubility in aqueous solution. *Langmuir.* 2014, V. 30, P. 3967–3970. [http://dx.doi.org/10.1021/la404976k](http://dx.doi.org/10.1021/la404976k)

24. Prylutskyy Yu. I., Ogloblya O. V., Eklund P., Scharff P. Electronic properties of carbon nanotubes with defects. *Synth. Met.* 2001, V. 121, P. 1209–1210. [http://dx.doi.org/10.1016/S0379-6779(00)00812-2](http://dx.doi.org/10.1016/S0379-6779(00)00812-2)

25. Ogloblya O. V., Prylutskyy Yu. I., Strzhemey Yu. M. Peculiarities of conductance of carbon nanotube-based quantum dots. *Int. J. Quantum Chem.*
26. Murdock M., Murdoch M. M. Compartment syndrome: a review of the literature. *Clin. Podiatr. Med. Surg.* 2012, V. 29, P. 301–310. [http://dx.doi.org/10.1016/j.cpm.2012.02.001](http://dx.doi.org/10.1016/j.cpm.2012.02.001)

27. Wang W. Z., Baynosa R. C., Zamboni W. A. Therapeutic interventions against reper-fusion injury in skeletal muscle. *J. Surg. Res.* 2011, V. 171, P. 175–182. [http://dx.doi.org/10.1016/j.jss.2011.07.015](http://dx.doi.org/10.1016/j.jss.2011.07.015)

28. Erkut B., Özyazıcıoğlu A., Karapolat B. S., Koğulları C. U., Keles S., Ateş A., Gundogdu C., Kocak H. Effects of ascorbic Acid, alpha-tocopherol and allopurinol on ischemia-reperfusion injury in rabbit skeletal muscle: an experimental study. *Drug Target Insights*. 2007, V. 2, P. 249–258.

29. Rácz I. B, Illyés G., Sarkadi L., Hamar J. The functional and morphological damage of ischemic reperfused skeletal muscle. *Eur. Surg. Res*. 1997, V. 29, P. 254–263. [http://dx.doi.org/10.1159/000129531](http://dx.doi.org/10.1159/000129531)

30. Bortolotto S. K., Morrison W. A., Messina A. The role of mast cells and fibre type in ischemia reperfusion injury of murine skeletal muscles. *J. Inflamm.* (Lond). 2004, V. 1, P. 1–7. [http://dx.doi.org/10.1186/1476-9255-1-2](http://dx.doi.org/10.1186/1476-9255-1-2)

31. Turócsi Z., Arányi P., Lukáts Á., Garbaisz D., Lotz G., Harsányi L., Szijártó A. Muscle
fiber viability, a novel method for the fast detection of ischemic muscle injury in rats. *PLoS One* 2014, V. 9, P. e84783.  
[http://dx.doi.org/10.1371/journal.pone.0084783](http://dx.doi.org/10.1371/journal.pone.0084783)

32. *Sternbergh W. C., Adelman B.* Skeletal muscle fiber type does not predict sensitivity to postischemic damage. *J. Surg. Res.* 1992, V. 53, P. 535–541.  
[http://dx.doi.org/10.1016/0022-4804(92)90103-7](http://dx.doi.org/10.1016/0022-4804(92)90103-7)

33. *Loerakker S., Oomens C. W., Manders E., Scha-ke T., Bader D. L., Baaijens F. P., Nicolay K., Strijkers G. J.* Ischemia-reperfusion injury in rat skeletal muscle assessed with T2-weighted and dynamic contrast-enhanced MRI. *Magn. Reson. Med.* 2011, V. 66, P. 528–537.  
[http://dx.doi.org/10.1002/mrm.22801](http://dx.doi.org/10.1002/mrm.22801)

34. *Carvalho A. J., McKee N. H., Green H. J.* Metabolic and contractile responses of fast and slow twitch rat skeletal muscles to ischemia and reperfusion. *Plast. Reconstr. Surg.* 1997, V. 99, P. 163–171.  
[http://dx.doi.org/10.1097/00006534-199701000-00025](http://dx.doi.org/10.1097/00006534-199701000-00025)

35. *Grace P. A.* Ischemia-reperfusion injury. *Br. J. Surg.* 1994, V. 81, P. 637–647.  
[http://dx.doi.org/10.1002/bjs.1800810504](http://dx.doi.org/10.1002/bjs.1800810504)

36. *Carvalho A. J., Hollett P., McKee N. H.* Recovery of synergistic skeletal muscle function following ischemia. *J. Surg. Res.* 1995, V. 59, P. 527–533.  
[http://dx.doi.org/10.1006/jsre.1995.1202](http://dx.doi.org/10.1006/jsre.1995.1202)

37. *Tidball J. G.* Mechanisms of muscle injury, repair, and regeneration. *Compr. Physiol.* 2011, V. 1, P. 2029–2062.  
[http://dx.doi.org/10.1002/cphy.c100092](http://dx.doi.org/10.1002/cphy.c100092)
38. Cuzzocrea S., Riley D. P., Caputi A. P., Salvemini D. Antioxidant therapy: a new pharmacological approach in shock, inflammation, and ischemia-reperfusion injury. *Pharmacol. Rev.* 2001, V. 53, P. 135–159.

39. Matheis G., Sherman M. P., Buckberg G. D., Habron D. M., Young H. H., Ignarro L. J. Role of L-arginine-nitric oxide pathway in myocardial reoxygenation injury. *Am. J. Physiol* . 1992, V. 262, P. H616–620.

40. Chen Y. W., Hwang K. C., Yen C. C., Lai Y. L. Fullerene derivatives protect against oxidative stress in RAW 264.7 cells and ischemia-reperfused lungs. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 2004, V. 287, P. R21–26. [http://dx.doi.org/10.1152/ajpregu.00310.2003](http://dx.doi.org/10.1152/ajpregu.00310.2003)