Long-term treadmill exercise induces neuroprotective molecular changes in rat brain

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1Unitat de Farmacologia i Farmacognòsia Facultat de Farmàcia, Institut de Biomedicina (IBUB), Universitat de Barcelona, Nucli Universitari de Pedralbes, Barcelona; 2Centros de Investigación Biomédica en Red de Enfermedades Neurodegenerativas (CIBERNED), Barcelona; and 3Department de Psiquiatria i Medicina Legal, Institut de Neurociències, Fac de Medicina, Universitat Autònoma de Barcelona, Barcelona, Spain

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Bayod S, del Valle J, Canudas AM, Lalanza JF, Sanchez-Roige S, Camins A, Escorihuela RM, Pallàs M. Long-term treadmill exercise induces neuroprotective molecular changes in rat brain. J Appl Physiol 111: 1380–1390, 2011. First published August 4, 2011; doi:10.1152/japplphysiol.00425.2011.—Exercise enhances general health. However, its effects on neurodegeneration are controversial, and the molecular pathways in the brain involved in this enhancement are poorly understood. Here, we examined the effect of long-term moderate treadmill training on adult male rat cortex and hippocampus to identify the cellular mechanisms behind the effects of exercise. We compared three animal groups: exercised (30 min/day, 12 m/min, 5 days/wk, 36 wk), handled but nonexercised (treadmill handling procedure, 0 m/min), and sedentary (nonhandled and nonexercised). Moderate long-term exercise induced an increase in IGF-1 levels and also in energy parameters, such as PGC-1α and the OXPHOS system. Moreover, the sirtuin 1 pathway was activated in both the exercised and nonexercised groups but not in sedentary rats. This induction could be a consequence of exercise as well as the handling procedure. To determine whether the long-term moderate treadmill training had neuroprotective effects, we studied tau hyperphosphorylation and GSK3β activation. Our results showed reduced levels of phospho-tau and GSK3β activation mainly in the hippocampus of the exercised animals. In conclusion, in our rodent model, exercise improved several major brain parameters, especially in the hippocampus. These improvements induced the upregulation of sirtuin 1, a protein that extends life, the stimulation of mitochondrial biogenesis, the activation of AMPK, and the prevention of signs of neurodegeneration. These findings are consistent with other reports showing that physical exercise has positive effects on hormesis.

moderate exercise; forced treadmill; neurodegeneration; sirtuin 1; mitochondrial biogenesis; tau

Several molecular systems, including neurotrophic factors, may contribute to the beneficial effects of the exercise on the brain. For example, brain-derived neurotrophic factor (BDNF) supports the survival and growth of many neuronal subtypes, including glutamatergic neurons (5, 8). This effect is sustained several weeks after exercise. BDNF increases neural plasticity within the hippocampus, resulting in improved learning and memory (10).

Moreover IGF-1, a growth factor structurally related to pro-insulin, is a potent survival factor for neurons and oligodendrocytes. Furthermore, IGF-1 participates in neuronal growth and differentiation in the brain. In addition, IGF-1 may be an upstream mediator of BDNF gene regulation, neurogenesis, and the sirtuin 1 pathway, and might thus contribute to the protection of the brain against injury (22). Peripheral IGF-1 initiates growth-factor cascades in the brain that can alter plasticity mechanisms and can also induce neuroprotective pathways (10, 21).

Sirtuin 1, a NAD+ dependent deacetylase, is a potential downstream target that mediates the neuroprotective effects of IGF-1 (18). Evidence indicates that the sirtuin 1 pathway regulates cell survival and rescues proteins in several neurodegenerative conditions (12). In mammals, sirtuin 1 is located in the nucleus, and it regulates p53, NF-κB, the FoxO family, PGC-1α, and other transcription factors via deacetylation. Thus sirtuin affects crucial pathways involved in cellular stress resistance and oxidative metabolism (27, 28, 30). Recently, it was reported that sirtuin 1 mediates AMP-activated protein kinase (AMPK) action on PGC-1α transcriptional activity, the expression of genes involved in mitochondrial and lipid metabolism, and oxygen consumption (2). AMPK is a metabolic sensor that is transiently activated in muscle by acute exercise (3). Interdependent regulation of sirtuin 1 and AMPK may provide a precise mechanism to influence energy homeostasis. It has also been proposed that sirtuin 1 and PGC-1α expression are independently regulated; however, although sirtuin 1 may be involved in mitochondrial biogenesis, it does not correlate closely with mitochondrial protein expression (4).

In addition, the expression of nicotinamide phosphoribosyltransferase (NAMPT), a rate-limiting step in the conversion of nicotinamide to NAD+, is found to be higher in rat muscle after exercise. All the data available indicate that sirtuin 1 is responsive to exercise and that this pathway modulates the adaptive mechanism triggered by exercise (17).

The dependence of cellular NAD+ links sirtuin 1 to the metabolic state of the cell (18). This observation is particularly relevant for neuronal function as cognitive impair-
ment during aging and in neurodegenerative diseases occurs in the presence of mitochondrial disturbances. Indeed, sirtuin 1 activation has been postulated as a neuroprotective strategy. In this regard, new data indicate that this deacetylase interacts with components of the autophagy machinery, and so this new mechanism would explain the contribution of sirtuin 1 to cell survival (19, 28) and provide a link between the function of this deacetylase and the overall cellular response to limited nutrients.

Here, we examine the effect of long-term treadmill exercise on sirtuin 1 pathway activity and on the molecular and cellular processes associated with bioenergetics and neurodegeneration in the rat cortex and hippocampus.

**METHODS**

*Animals and general procedure.* Twenty-nine male Sprague-Dawley rats aged 5 wk at the beginning of the experiment were used. All rats were obtained from the Servei d’Estabulari (Universitat Autònoma de Barcelona). Animals were housed two per cage and had free access to food and water. They were maintained under a 12-h light-dark cycle (lights on at 0800) and standard temperature (22 ± 2°C). Rats were semi-randomly distributed into three experimental groups, balancing the total body weight: exercised (EXE; n = 12, 95.49 ± 3.38 g), control (NoEXE; n = 9, 102.24 ± 5.2 g), and sedentary (SED; n = 8, 95.75 ± 4.81 g) groups. At the end of the experiment, blood was obtained by intracardiac injection. The animals were then killed by decapitation between 0900 h and 1200. Eight-week-old male rats (n = 6) were also killed on the same day to include young controls in the analysis. The brain was immediately removed and dissected into cortex and hippocampus. Brain tissues were frozen in powdered dry ice and maintained at −80°C until use. In addition, four brains from each group were processed for immunohistochemical analysis. Briefly, the tissue was fixed in methacarn and processed for paraffin-embedded immunohistochemistry. The experimental protocol was approved by the Ethics Committee of the Universitat Autònoma de Barcelona and complied with “Principles of laboratory animal care” and the European Communities Council Directive (86/609/EEC).

*Exercise regime.* A treadmill consisting of three parallel runways (45 cm long, 11 cm wide, and 12 cm deep) was used. The apparatus was placed at an inclination of 0° in the cage. Exercise sessions were conducted between 1330 and 1630, 4–5 days/wk for 36 wk. Neither electrical shock nor physical prodding were used to force training. On the first day, the rats were placed in the treadmill for 30 min without running to become habituated to the apparatus and to diminish exercise-induced stress during the following days. EXE and NoEXE groups were weighed every day before the 30-min treadmill session. For the EXE group, the treadmill started at a speed of 4.2 m/min and increased progressively by 1 m/min every 30 s to a speed of 12 m/min (which was reached between minutes 3 and 12). NoEXE rats were
placed individually on another treadmill (0 m/s) for the same number of sessions and the same duration as the EXE rats. Thus control and exercised rats were handled in the same manner and spent the same amount of time out of the home cage. The SED group was handled once a week for cage cleaning and tail marking. Two rats were excluded from the experiment because they showed signs of distress and did not run.

**Brain isolation and Western blot analysis.** Tissues samples were homogenized in lysis buffer containing phosphatase and protease inhibitors (Cocktail II, Sigma). The protein concentration in tissue samples was determined by the Bradford method. Protein (20 μg) was separated by SDS-PAGE (5–15%) and transferred to PVDF membranes (Millipore). The membranes were blocked in 5% nonfat milk in TBS containing 0.1% Tween 20 (TBS-T) for 1 h at room temperature, followed by an overnight incubation at 4°C with antibodies diluted in TBS-T and 5% BSA sirtuin 1 (1:1,000; Millipore), p53 (1:1,000; Cell Signaling), acetylp53 (1:500; Abcam), NAMPT (1:1,000; Abcam), AMPKα (1:500; Cell Signaling), p-AMPKα Thr172 (1:500; Cell Signaling), tau (1:5,000; Biosource), p-tau Ser396 (1:4,000; Biosource), p-GSK3β Tyr172 (1:1,000; Upstate), GSK3β (1:1,000; Cell Signaling), PGC-1α (1:500; Cayman Chemical), OXPHOS cocktail (1:500; MitoSciences), porin (1:500; MitoSciences), synaptophysin (1:500; Abcam) GADPH (1:2,000; Millipore), and β-actin (1:20,000; Sigma). Membranes were then washed and incubated with secondary antibodies for 1 h at room temperature. Protein bands were visualized using a chemiluminescence detection kit (Amersham Biosciences). Band intensities were quantified by densitometric analysis, and values were normalized to β-actin or GAPDH expression.

**Immunohistochemistry and image acquisition.** Tissue samples were deparaffinized in xylene and hydrated through a descending ethanol gradient. Afterward, the brain sections were rehydrated with PBS for 5 min before being blocked and permeabilized with PBS containing 1% bovine serum albumin (BSA, Sigma-Aldrich) and 0.1% Triton-X-100 (Sigma-Aldrich) for 20 min. They were then washed twice for 5 min in PBS and incubated with the primary antibodies (see below) overnight at 4°C. After an additional wash, tissues were incubated with secondary antibodies (see below) for 1 h at room temperature. Tissues were washed again, and nuclear staining was performed by incubating slides in Hoechst (H-33258, Fluka, Madrid, Spain) reagent.

Fig. 3. Representative Western blots and adjusted values for the mitochondrial electron transport chain complexes in cortex from YOUNG, EXE, NoEXE, and SED animals. Images show representative Western blot and bar graph obtained from semi-quantitative image analysis, as described in MATERIALS AND METHODS. Data represent means ± SD of 6–8 rats. $P < 0.05$ vs. YOUNG; *$P < 0.05$ vs. SED; #P < 0.05 vs. NoEXE.
at 2 μg/ml in PBS for 10 min at room temperature in the dark. Finally, slides were washed, mounted using fluoromount G, allowed to dry overnight at room temperature, and stored at 4°C in the dark. Immunostained controls were performed by incubation with PBS instead of the primary antibody or instead of both antibodies. Rabbit polyclonal anti-prohibitin (1:50; Santa Cruz) was used as a mitochondrial marker. The AlexaFluor 555 donkey anti-rabbit IgG (1:250; Invitrogen, Carlsbad, CA) was used as secondary antibody. Images were taken with a fluorescence laser microscope (BX41, Olympus, Germany) at ×20 magnification. All images were acquired with the same microscope, laser, and software settings.

**IGF-1 determination.** Serum was obtained from heparinized blood samples centrifuged (3,500 rpm, 10 min, room temperature) immediately after intracardiac extraction. Serum samples were maintained at −80°C until use. Serum IGF-1 was determined by ELISA kit (Mouse/Rat Insulin-like Growth Factor-I; Mediagnost, IGF-I Ela E25) following the manufacturer's recommendations.

**Data analysis.** Data are expressed as means ± SD from 6–8 samples. In all cases, data were analyzed by ANOVA followed by post hoc Tukey-Kramer multiple-comparison tests. *P* values of <0.05 were considered significant.

**RESULTS**

**IGF-1 plasma levels and body weight.** At the end of the experimental protocol, none of the experimental groups registered significant changes in weight (data not shown).

IGF-1 serum levels were significant higher in YOUNG than in SED animals (Fig. 1). Levels of IGF-1 were higher in EXE than in NoEXE and SED rats (Fig. 1). A significant increase was also detected in the NoEXE group compared with SED animals. In both groups (EXE and NoEXE), IGF-1 levels reached levels observed in YOUNG rats.

**Bioenergetic parameters.** Immunohistochemistry with prohibitin as a mitochondrial marker revealed a weaker presence of mitochondria in the dentate gyrus of the SED animals than in the other groups (Fig. 2). Analysis of the OXPHOS system demonstrated that some mitochondrial complexes were increased in the hippocampus and cortex of EXE animals. Significant increases were found in complex III and V in the cortex of these animals (Fig. 3), whereas increases in complexes I, IV, and V were detected in the hippocampus of EXE animals compared with YOUNG, SED, and NoEXE animals.

![Image](http://www.jap.org/image.png)

*Fig. 4.* Representative Western blots and adjusted values for the mitochondrial electron transport chain complexes in hippocampus from YOUNG, EXE, NoEXE, and SED animals. Images show representative Western blots and bar graph obtained from semi-quantitative image analysis as described in MATERIALS AND METHODS. Data represent means ± SD of 6–8 rats. $P < 0.05$ vs. YOUNG; *$P < 0.05$ vs. SED; #$P < 0.05$ vs. NoEXE.
were found in hippocampus of EXE rats compared with SED animals (Fig. 4). No significant differences were found between NoEXE and SED animals in any cerebral area studied. Moreover, AMPK activation was detected both in cortex and hippocampus in the EXE group, as shown by greater levels in Thr\textsuperscript{172} phosphorylation compared with SED and NoEXE animals. No differences in AMPK activation were observed between SED and NoEXE (Fig. 5, A and B).

Fig. 5. Changes in AMPK phosphorylation (p-AMPK/Thr\textsuperscript{172}) were detected in the cortex (A) and hippocampus (B) of EXE, but not NoEXE or SED animals. Higher levels were also found in EXE animals for AMPK phosphorylation than for NoEXE animals both in cortex (A) and hippocampus (B). Cortex levels of PGC-1\(\alpha\) were higher in EXE and NoEXE than in SED animals (C), and no changes were found in hippocampus (D). Cortex levels of PGC-1\(\alpha\) were also higher in the EXE compared with the NoEXE group. Images show representative Western blots and bar graph obtained from semi-quantitative image analysis as described in MATERIALS AND METHODS. Data represent means \(\pm\) SD of 6–8 rats. $P < 0.05$ vs. YOUNG; *$P < 0.05$; **$P < 0.01$ vs. SED; $#P < 0.05$; ##$P < 0.01$ vs. NoEXE.
Regional differences were found for PGC-1α. Although no significant differences were detected in the hippocampus (Fig. 5D), an increase in total protein was found in the cortex (Fig. 5C) of the EXE group compared with NoEXE and SED animals. Also, significant differences in PGC-1α between NoEXE and SED were found in the cortex (Fig. 5C).

_Sirtuin 1 pathway._ Immunodetection of sirtuin 1 in the cortex and hippocampus of EXE and NoEXE animals showed a significant increase compared with SED rats (Fig. 6, A and C). These results correlated with a significant decrease in p53 acetylation in EXE and NoEXE animals in the same areas. Furthermore, a higher sirtuin 1 expression and a lower p53 acetylation were found to be significant between the cortex of EXE and NoEXE animals (Fig. 6, A and B). Given the relationship between the sirtuin 1 pathway and aging, we also examined the sirtuin 1 and acetylated p53 in a group of

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**Fig. 6.** Sirtuin 1 levels and its acetylated substrate p53 in YOUNG, EXE, NoEXE, and SED animals. Sirtuin 1 levels were higher in EXE and NoEXE than in SED, and in a parallel fashion Ac-p53 expression was lower in these groups compared with SED. Images show representative Western blots and bar graph obtained from semi-quantitative image analysis of cortex (A and B) and hippocampus (C and D) as described in MATERIALS AND METHODS. Data represent means ± SD of 6–8 rats. $P < 0.05$ vs. YOUNG; *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$ vs. SED; #P < 0.05 vs. NoEXE.
young (8-wk-old) rats. Significant differences in the expression of sirtuin 1 in the hippocampus and p53 acetylation levels in the cortex were detected between young and SED animals, thus corroborating the contributing role of the sirtuin 1 pathway to aging (Fig. 6, B and C). However, although sirtuin 1 activity is dependent on the NAD\(^+\)-to-NADP ratio, we did not detect changes in NAMPT levels (a key regulator of the NAD\(^+\) production) in any experimental groups (Fig. 7).

Neuroprotective role of treadmill exercise in rats. We studied the levels of tau hyperphosphorylation and GSK3\(\beta\) as measures of the induction of neuroprotection after exercise. No changes were detected in tau phosphorylation or GSK3\(\beta\) activity in the cortex of EXE or NoEXE animals (Fig. 8, A and C). However, in the hippocampus, the degree of tau phosphorylation (Ser\(^{396}\)) was lower in EXE animals than in the NoEXE and SED groups (Fig. 8B). In addition, GSK3\(\beta\) activation was higher in the SED group compared with the EXE and NoEXE animals, as shown by the increase in the phosphorylated form of GSK3 in Tyr\(^{216}\) (Fig. 8D). Moreover, these two proteins were also measured in the cortex and hippocampus of the young animals. Lower levels in tau phosphorylation were found in young animals compared with adult animals with the exception of the hippocampus of the EXE group, where no significant differences were reached (Fig. 8, A and B). On the other hand, young rats showed less GSK3\(\beta\) activation (Fig. 8, C and D) in the two cerebral areas studied.

To finish with, we also measured the levels of synaptophysin, a marker of neurotransmission. EXE and NoEXE rats showed higher synaptophysin expression in the cortex than SED animals. Conversely, a significant increase in this parameter was observed only in the hippocampus of EXE rats (Fig. 9). This observation explains the differential effect of exercise in this cerebral area.

**DISCUSSION**

Clinical literature has long recognized that exercise enhances overall health and brain function (16, 34). Recent studies reinforce the hypothesis that exercise benefits brain function by inducing BDNF and other molecules that mediate improvements in neuronal structure, facilitate synaptic transmission, and offer neuroprotective actions in several physiological (aging) and pathological (neurodegenerative diseases) conditions (22, 33). One of the most promising pathways implicated in enhanced neuronal conditions is sirtuin 1 (31). In this regard, few studies have addressed the expression and activity of this molecule or that of sirtuin 6, which are related to forced exercise (17).

IGF-1 increases in plasma and brain after exercise, and at least part of the increase in the brain reflects increased transport from the periphery across the blood-brain barrier. Peripheral IGF-1 initiates growth-factor cascades in the brain that can alter on-going plasticity mechanisms or neuroprotective pathways (20, 33). In our experimental conditions, the EXE group showed higher serum IGF-1 levels than NoEXE and SED animals, thereby indicating a positive effect of long-term moderate exercise. Notably, exercise alters tissue metabolism, resulting in reduced fat accumulation and increased insulin.
sensitivity. This action thus contributes to delaying the onset of age-related diseases (13).

In skeletal muscle, exercise promotes mitochondrial biogenesis and alterations in energy metabolism through increases in PGC-1α expression (14). Thus mitochondrial biogenesis is a possible target of the molecular changes induced by exercise (9, 15). The long-term moderate exercise in this study altered the mitochondrial pattern in the brain; SED animals presented
less immunoreactivity for prohibitin (a mitochondrial marker) in the dentate gyrus, a zone of the brain characterized by a high rate of neurogenesis. Consistently, increases in complex V in the cortex and hippocampus were found, whereas complex III in the cortex and complexes I and IV in the hippocampus were also higher in EXE rats than in the other two groups. Moreover, these results are consistent with those of others studies in rodents that described an increase in mitochondrial biogenesis in other tissues after exercise (14, 15). Accordingly, we found that activation of AMPK was higher in the EXE rats than in the other two groups.

Endurance training and in vivo chronic contractile activity are paradigms that dramatically increase mitochondrial biogenesis, mediated in part through the elevation in PGC-1α expression and activation in muscle and heart (38). We detected an increase in PGC-1α in the cortex of EXE rats. Suwa and coworkers (31) were the first to demonstrate that skeletal muscle sirtuin 1 protein expression increases in rats in response to exercise. They found that sirtuin 1 and PGC-1 protein levels were higher and correlated positively with mitochondrial components (31). Furthermore, Canto and coworkers (2) demonstrated that the activity of PGC-1α is finely tuned by AMPK and sirtuin 1, as a mechanism for energy homeostasis under long-term physical exercise (18).

It has recently been proposed that sirtuin 1 expression is more closely related to mitochondrial biogenesis than PGC-1α (4). We found that long-term moderate exercise, comparable to rapid walking or slow running in humans, induced a significant increase in sirtuin 1 expression in the rat cortex and hippocampus compared with the SED group. The differences were also significant compared with the cortex of NoEXE group, thus indicating that part of the effect observed on sirtuin 1 expression was due mainly to moderate running exercise per se and not only to the handling procedure involved in the treadmill training protocol. The increase in sirtuin 1 expression correlated with a reduction in the acetylated form of p53, one of the most important substrates of this deacetylase. Aging is one of the physiological processes associated with sirtuin 1. We also studied the activation of the sirtuin 1 pathway in young animals. As expected, significant differences were found for sirtuin 1 and acetylated p53 levels when compared with adult SED animals.

Some authors reported higher levels of NAMPT and the limiting enzyme of NAD+ processing in the skeletal muscle of sedentary subjects after 3 wk of exercise training, and they also described that NAMPT correlated with mitochondrial content (7). Conversely, we found no increase in the NAD+ to NADP ratio as a result of higher sirtuin 1 activity since no changes in the limiting enzyme of NAD+ processing (NAMPT) were found in our experimental conditions. However, the increase in AMPK activation, which acts as a sensor of energy requirements and in sirtuin 1 activity, was accompanied by enhanced deacetylase activity in our experimental conditions.

Globally, these results show that exercise increases energy availability in brain and activates a prosurvival pathway, namely sirtuin 1 (23). Thus an improvement in neuronal function and neuroprotection can be deduced, because neuroprotection is also linked to energy disposal. We examined the degree of tau phosphorylation and GSK3β activation as indicators of the prevention of neurodegeneration since hyperphosphorylation of tau is responsible for several degenerative con-

Fig. 9. Synaptophysin expression in the cortex (A) and hippocampus (B). The expression of synaptophysin was significantly higher in the cortex of EXE and NoEXE animals than in SED rats. However, in the hippocampus, higher levels appeared only in EXE animals. Images show representative Western blots and bar graph obtained from semi-quantitative image analysis, as described in MATERIALS AND METHODS. Data represent means ± SD of 6–8 rats. $ P < 0.05$ vs. YOUNG; $^*P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$ vs. SED; $^{##}P < 0.01$ vs. NoEXE.
conditions in the brain (25). Long-term moderate exercise prevented tau hyperphosphorylation and rendered GSK3β inactive, two processes observed in the SED animals. The preventive effect of long-term moderate exercise on these parameters was significant in the hippocampus, the main area of the brain associated with learning and memory, and were more similar to the profile of young animals. Moreover, exercise also induced an increase in synaptophysin, especially in the hippocampus, in agreement with Dietrich et al. (9), who described that exercise induced an increase in mitochondria number and dendritic spine synapse in hippocampus, mainly in CA1 and dentate gyrus. Thus moderate exercise would ameliorate the development of ongoing neurodegeneration processes by preventing tau hyperphosphorylation, GSK3β activation, and synaptophysin loss.

Regarding the treadmill handling used for the NoEXE control group, this procedure has been reported to modify learning performance and neuropsychiatric markers in the hippocampus (24). The results of our experiments showed that sirtuin 1 and other parameters, such as IGF-1, were lower in the SED group than in the other two groups. This observation indicates that these parameters can be affected by both types of intervention, which is also consistent with a report by other authors (24). However, it is noteworthy to say that sirtuin 1 and IGF-1 levels were higher in the EXE than in the NoEXE group, thus emphasizing the positive effect of exercise on these two parameters. Moreover, AMPK activation, mitochondrial activity, and tau phosphorylation determination were affected only in the handling plus exercise group. Thus exercise per se, but not handling, contributed to these changes.

In conclusion, although the benefits of moderate exercise on brain functions are controversial, in our rodent model, exercise induced improvements in several major brain parameters, especially in the hippocampus. Examples of these improvements are as follows: upregulation of molecules that extend life, such as sirtuin 1; stimulation of mitochondrial biogenesis in dentate gyrus; activation of AMPK; and prevention of signs of neurodegeneration. These observations support the findings of several reports describing that exercise produces various major benefits related to hormesis and that the mild oxidative stress produced during exercise results in favorable adaptations that protect organisms against more severe stress or disorders.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

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