Diabetes impairs exercise training-associated thioredoxin response and glutathione status in rat brain

Zekine Lappalainen,1 Jani Lappalainen,1 Niku K. J. Oksala,1,2,3 David E. Laaksonen,1,4 Savita Khanna,5 Chandan K. Sen,5 and Mustafa Atalay1

1Institute of Biomedicine, Physiology, University of Kuopio, Kuopio, Finland; 2Institute of Clinical Medicine, Surgery, Kuopio University Hospital, Kuopio, Finland; 3Division of Vascular Surgery, Department of Surgery, Tampere University Hospital, Tampere, Finland; 4Institute of Clinical Medicine, Internal Medicine, Kuopio University Hospital, Kuopio, Finland; and 5Laboratory of Molecular Medicine, Department of Surgery, Davis Heart and Lung Research Institute, The Ohio State University Medical Center, Columbus, Ohio

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Lappalainen Z, Lappalainen J, Oksala NK, Laaksonen DE, Khanna S, Sen CK, Atalay M. Diabetes impairs exercise training-associated thioredoxin response and glutathione status in rat brain. J Appl Physiol 106: 461–467, 2009. First published December 12, 2008; doi:10.1152/japplphysiol.91252.2008.—Regular exercise plays an important preventive and therapeutic role in oxidative stress-associated diseases such as diabetes and its complications. Thiol antioxidants including thioredoxin (TRX) and glutathione (GSH) have a crucial role in controlling cellular redox status. In this study, the effects of 8 wk of exercise training on brain TRX and GSH systems, and antioxidant enzymes were tested in rats with or without streptozotocin-induced diabetes. We found that in untrained animals, the levels of TRX-1 (TRX1) protein and activity, and thioredoxin-interacting protein (TXNip) were similar in diabetic and nondiabetic animals. Exercise training, however, increased TRX1 protein in nondiabetic animals without affecting TXNip levels, whereas diabetes inhibited the effect of training on TRX1 protein and also increased TXNip mRNA. In addition, the proportion of oxidized glutathione (GSSG) to total GSH was increased in animals with diabetes, indicating altered redox status and possibly increased oxidative stress. Glutathione peroxidase-1 (GPX1) levels were not affected by diabetes or exercise training, although diabetes increased total GPX activity. Both diabetes and exercise training decreased glutathione reductase (GRD) activity and cytosolic superoxide dismutase (Cu,Zn-SOD) levels. Nevertheless, diabetes or training had no effect on Cu,Zn-SOD mRNA, Mn-SOD protein, total SOD activity, or catalase mRNA, protein, or activity. Our findings suggest that exercise training increases TRX1 levels in brain without a concomitant rise in TXNip, and that experimental diabetes is associated with an incomplete TRX response to training. Increased oxidative stress may be both a cause and a consequence of perturbed antioxidant defenses in the diabetic brain.

Endogenous thiol antioxidants thioredoxin (TRX) and glutathione (GSH) are potent protein disulfide reductases that have a crucial role in controlling cellular redox status by participation in many thiol-dependent cellular reductive processes and play an important role in antioxidant defense and protecting cells from various types of stresses (22, 36, 43). Previously, TRX and GSH were considered clearly distinct systems. Nevertheless, loss of cellular TRX is known to result in elevated GSH levels, indicating a link between the TRX system and GSH metabolism (11). In addition, other enzymatic antioxidants, including copper-zinc superoxide dismutase (Cu,Zn-SOD), manganese superoxide dismutase (Mn-SOD) (37, 43) and catalase (CAT) (38, 43), are also key components of the endogenous antioxidant protection.

Diabetes may make tissues more susceptible to oxidative stress (7). In brain, the TRX system comprising TRX and NADPH-dependent TRX reductase (TrxR) may provide protection during various hypoxic or ischemic events (58, 63, 64), although also decreased TRX activity has been reported in diabetes without significant changes in the levels of TRX protein (53). Importantly, the expression of thioredoxin-interacting protein (TXNip), an endogenous inhibitor of TRX (42), was markedly increased in animals with diabetes (53).

Regular exercise improves brain function and can play an important preventive and therapeutic role in oxidative stress-associated diseases such as diabetes and its complications (48, 50). The effects of regular exercise in brain are complex and may include neurogenesis and increased capillarization (2, 3, 9, 13, 32), decreased oxidative damage, and enhanced activity of antioxidant enzymes, including SOD and glutathione peroxidase (GPX) (16, 59). Although the available studies on TRX in exercise are scanty, TRX mRNA expression was found to be increased in mouse peripheral blood mononuclear cells at 12 and 24 h after acute exhaustive exercise (66). However, information regarding the effect of regular exercise training on brain TRX system or the cross-talk between TRX and GSH systems has not been available. The objective of the present study was to investigate whether experimental diabetes impairs TRX and GSH systems in brain and to assess whether these systems can be upregulated using exercise training to improve cellular redox status and antioxidant protection in brain.

Address for reprint requests and other correspondence: M. Atalay, Institute of Biomedicine, Physiology, Univ. of Kuopio, P.O. Box 1627, FIN-70211 Kuopio, Finland (e-mail: mustafa.atalay@uku.fi).

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MATERIALS AND METHODS

Animals. Twelve-week-old outbred male Wistar rats were used in the study. The animals (n = 24) were maintained at 22 ± 2°C with 12:12-h light-dark cycles and had free access to standard rat chow and water. Animal care and experimental procedure were in accordance with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85–23, Revised 1985). The experimental protocol was approved by the Ethics Committee for laboratory animal research of University of Kuopio, Finland.

Preparation of diabetic rats. The animals were randomly assigned to nondiabetic (n = 12) and diabetic (n = 12) groups. Diabetes was then induced by a single intraperitoneal injection of streptozotocin (60 mg/kg, prepared in 0.1 mol/l citrate buffer, pH 4.5) as described (7) to destroy pancreatic beta cells as an experimental model of type 1 diabetes (69). Glucosuria was confirmed using test strips (BM-Test-5L, Boehringer-Mannheim) 1 wk after the streptozotocin injection, and routinely repeated once per week throughout the study. In addition, blood glucose levels were measured at the end of the study in trunal blood collected immediately after decapitation using a commercial kit (Gluc-o-quant Glucose/HK, Boehringer-Mannheim) employing the hexokinase reaction, as previously reported (19). Animals with sustained diabetes (glucosuria of at least 20 mmol/l, 2 wk after the streptozotocin injection) and the nondiabetic control animals were further divided into respective training (n = 6) and nontraining (n = 6) groups.

Training protocol. The rats were trained on a treadmill for 8 wk, 5 days/wk (1.5 h/day) as previously described (7). The animals tolerated the training well and were able to increase running distance and intensity according to the training protocol throughout the study. Response to exercise training was confirmed by increased skeletal muscle citrate synthase activity as previously reported (7). Response to exercise training was confirmed by increased skeletal muscle citrate synthase activity as previously reported (7).

Tissue harvesting. The animals were killed by decapitation at rest or ~72 h after the last training session. Following decapitation, whole brains (cerebrum) of the animals were quickly removed, rinsed in ice-cold saline, blotted, placed in liquid nitrogen, and stored at −70°C until use.

Analysis of antioxidant enzyme proteins by Western blot. The expression of antioxidant enzymes at protein level was analyzed by a Western blot technique. First, the frozen whole brains were pulverized and homogenized under liquid nitrogen with a mortar and sonicated in expression of antioxidant enzymes at protein level was analyzed by a quantitative real-time RT-PCR was applied. Briefly, 100 mg of whole brain was first homogenized with Ultra-Turrax (Janke and Kunkel), and total cellular RNA was isolated using the Eurozol reagent (Euroclone, West York, UK) according to manufacturer’s instructions. Nucleic acid concentrations were determined by NanoDrop spectrophotometer (NanoDrop Technologies, Wilmington, DE), and their integrity was checked with gel electrophoresis. One microgram of RNA from each sample was then converted to cDNA using SuperScript III reverse transcriptase (Invitrogen, Carlsbad, CA) and oligo(dT) primers (Promega, Madison, WI). For PCR primer design, the annotated nucleotide sequences were retrieved from GenBank database (National Center for Biotechnology Information, Bethesda, MD) and set not to amplify genomic DNA. The primers were synthesized by oligomer GCS (Helsinki, Finland) as follows (with GenBank accession number): TRX-1 (NM_0053800) forward primer (-F) 5'-TTCTTGAAGATGACGCGTTGATGC-3' and reverse primer (-R) 5'-AGAAAGCTCCCAAACCCTTGGAC-3'; TXNip (NM_00108767)-F 5'-CTCTTGACACAAGCTACGGA-3' and TXNIP-R 5'-CAACGACCATTTCCTCCTGGAG-3'; GRX-1 (NM_022278)-F 5'-CTGGTGTCTCGTG-AATTGTG-3' and GRX-1-R 5'-AAGACCCGAGAAGCTTCTT-CTGG-3'; Cu,Zn-SOD (NM_012880)-F 5'-CATCTTTGCGAGACGTGGTGC-3' and Cu,Zn-SOD-R 5'-GGCTAAAGCGGCTGCTG-3'; CAT (NM_012520)-F 5'-TTCAGAGAGACGCTCAAG-3' and CAT-R 5'-CATTTGTTGCTGCTG-3'; GRX-1 (NM_022278)-F 5'-CTTCTGTGCTTGAAGAGAGAAAGGA-3' and GRX-1-R 5'-TCCACCCTGGATCGAGACTGTC-3'. For PCR analysis, the samples were amplified in duplicate using Brilliant SYBR Green Master Mix (Stratagene, La Jolla, CA) with 200 nM of gene-specific primers and run on Mx3000P System (Stratagene) with the following program: a 10-min preincubation at 95°C, followed by 40 cycles of 1 s at 95°C, 20 s at 60°C, and 25 s at 72°C. The data were normalized relative to expression of CypB by the previously introduced algorithm (46). Unique amplification products and absence of primer-dimers were evaluated by melt curve analysis.

Assays for glutathione levels and antioxidant enzyme activity. For the determination of total (TGSH) and oxidized glutathione (GSSG), the whole brains were first homogenized on ice in brief burst by Ultra-Turrax in a 1:6 (wt/vol) dilution with cold 5% metaphosphoric acid, centrifuged at 10,000 g for 15 min at 4°C, and the supernatants were collected and stored at −80°C. On the day of measurement, the supernatants were diluted in water and measured spectrophotometrically for TGSH and GSSG (55). Total GPX activity was determined with cumene hydroperoxide as substrate (67); glutathione reductase (GRD) activity was determined as described by Carlberg and Mannervick (10) in the presence of 50 mM Tris (GRD) activity was determined as described by Carlberg and Mannervick (10) in the presence of 50 mM Tris-HCl buffer with 1 mM EDTA, 2 mM NADPH, and 20 mM GSSG by monitoring the decrease in absorbance at 340 nm due to the oxidation of NADPH per minute. TXR1 and TXR reductase-1 (TrxR1) activities were assayed using a commercially available kit according to manufacturer’s instructions (IMCO). Total SOD activity was determined according to Beuchamp and Fridovich (8) and CAT activity essentially as described by Aebi (4). Results are expressed as units (U) per milligram of protein, as nanomoles per minute per milligram of protein, or as micromoles per gram wet weight, when appropriate.

Statistics. All calculations were performed using SPSS software (SPSS, Chicago, IL). Differences in continuous variables between the groups were assessed using Student’s t-test. The effect of diabetes and endurance training was tested with two-way ANOVA. Correlation analyses were performed using the Pearson product-moment correlation coefficient. Statistical significance was considered at P < 0.05. Data are represented as means ± SE unless otherwise stated.
RESULTS

Effect of diabetes and training on blood glucose and brain TRX system. In animals with diabetes, blood glucose levels at rest were higher than in the nondiabetic rats (19.2 ± 3.8 vs. 8.8 ± 0.7 mmol/L, respectively) (P < 0.001) and those described in rats without diabetes (7.0 ± 1.0 mmol/L) (51). TRX1 and TXNip levels did not differ between nondiabetic and diabetic animals, but exercise training increased TRX1 protein (P = 0.024) without affecting TXNip levels (Fig. 1). On the other hand, diabetes inhibited the effect of training on TRX1 protein and also increased TXNip mRNA (P = 0.027), although training or diabetes had no effect on TRX1 mRNA, TXNip protein, or TRX1 and TrxR1 activities (Fig. 1 and Table 1).

Effect of diabetes and training on glutathione and glutathione-related enzymes. Diabetes had no effect on TGSH levels but increased GSSG and the GSSG/TGSH ratio (P = 0.004 and P < 0.0001, respectively), whereas exercise training had no effect on these values (Fig. 2).

GPX activity was significantly increased by diabetes (P = 0.003), but GPX1 protein levels were not affected by diabetes or exercise training (Fig. 3). On the other hand, both diabetes and exercise training significantly decreased GRD activity (P < 0.0001 and P < 0.0001, respectively), without affecting GRX1 protein and mRNA levels (Fig. 3 and Table 1).

Effect of diabetes and training on other antioxidant enzymes. We also analyzed the effect of diabetes and exercise training on Cu,Zn-SOD, Mn-SOD, and CAT protein, and total SOD activity. The levels of Cu,Zn-SOD protein were increased in diabetic animals (P = 0.048), and exercise training increased this protein in both diabetic and nondiabetic animals (P = 0.005) (Fig. 4). However, neither diabetes nor exercise training had any effect on Cu,Zn-SOD mRNA, Mn-SOD protein, total SOD activity, or CAT (Fig. 4 and Table 1).

Correlations between TRX protein and antioxidant enzymes. In nondiabetic untrained animals, TRX1 protein showed a strong positive correlation with Mn-SOD (r = 0.90) and GPX1 protein (r = 0.92), whereas in exercise-trained animals, TRX1 correlated strongly with Cu,Zn-SOD (r = 0.93) and Mn-SOD (r = 0.86), TXNip (r = 0.83), GRX1 (r = 0.82), and CAT (r = 0.96), but not with GPX1 (r = 0.148). Interestingly, GRD activity showed a strong negative correlation with TRX1 protein in exercise-trained animals (r = −0.90).

In untrained animals with diabetes, a significant correlation was only observed between TRX1 protein and total SOD activity (r = 0.88), and Cu,Zn-SOD protein (r = 0.96). In exercise-trained animals with diabetes, TRX1 showed a significant positive correlation only with CAT protein (r = 0.97) and a negative correlation with CAT activity (r = −0.98). No significant correlations with TRX1 and GSH or GSSG/GSH ratio were found in either diabetic or nondiabetic animals.

DISCUSSION

In this study we showed that the levels of TRX1 and TXNip protein in brain were not affected by experimental diabetes. Importantly, we report that exercise training increased TRX1 protein in nondiabetic animals without affecting TXNip levels, whereas diabetes inhibited the effect of training on TRX1 protein and also increased TXNip mRNA levels. Consistent with our results, TRX mRNA levels were previously shown to be increased after acute exercise in peripheral blood (66). Data on brain tissue and the interaction of diabetes and exercise training have not been available until now.

TRX plays an essential role in cell function and protection by limiting oxidative stress directly via its antioxidant effects, and also indirectly by protein-protein interactions with key signaling molecules. This aspect may be crucial for the maintenance of redox control and to trigger physiological adaptations during strenuous physical exercise when peroxide production is increased and redox control circuits are prone to be disrupted (28). TRX expression is affected by stress and protects against oxidative stress-induced apoptosis (40). Siu et al. (57) reported unaltered TRX activity in brain in rats in response to ischemia, although TRX protein levels were increased and sustained during ischemia (57). We also observed that TRX1 or TrxR1 enzyme activities were not affected by diabetes or exercise training. Thus elevations of TRX1 protein in response to exercise training may serve a normal physiological function in brain tissue, without concomitant increase in TRX1 or TrxR1 activity. On the other hand, it has been suggested that TrxR may be transiently or permanently inactivated by oxidants such as hydrogen peroxide (6).

Our findings on increased TXNip mRNA levels in diabetic animals are in partial agreement with a previous report (47), in which TXNip mRNA and also protein levels were increased in peripheral neuronal cells of diabetic animals, whereas no difference in TRX was observed (47). An increased TXNip expression has been described in response to high glucose concentrations in human pancreatic islets (56), aortic smooth muscle cells (53), kidney mesangial cells (31), adipocytes and skeletal muscle cells (45), and also in vivo in streptozotocin-induced diabetic mice kidneys (31) and in the skeletal muscle of prediabetic and diabetic humans (45). However, TRX was unaffected by glucose (53). Furthermore, the glucose-induced
diabetic and diabetic rat brain levels of total glutathione (TGSH), oxidized glutathione (GSSG), and GSSG/TGSH ratio in animals with diabetes indicates altered redox status and increased oxidative stress. GSH is the most abundant low-molecular-weight thiol in eukaryotic cells and has been widely used as an oxidative stress marker. It is not known, however, to what extent GSH and TRX systems would appear to compete with each other for intracellular reducing equivalents, recent data suggest that this may be an important regulatory mechanism of cellular redox processes. Therefore, the increased binding of TXNip to TRX may account for the functional inhibition of TRX activity and mediates oxidative stress in diabetes (29, 53). This is of importance as TRX has functional inhibition of TRX activity and mediates oxidative stress in diabetes (29, 53) and is suppressed by insulin signaling (45). Although no significant effect of diabetes or exercise training on total GSH levels were found in the present study, the increased levels of GSSG and the GSSG/GSH ratio in animals with diabetes indicates altered redox status and increased oxidative stress. GSH is the most abundant low-molecular-weight thiol in eukaryotic cells and has been widely used as an indicator of the cellular redox state (52). Despite the fact that GSH and TRX systems would appear to compete with each other for intracellular reducing equivalents, recent data suggest that there may lay an underlying specificity and organization of the GSH and TRX-dependent redox-signaling events (27). Furthermore, GRXs catalyze introduction and removal of GSH, and an isotype of TrxR has activity toward both TRX and GSH (65). It is not known, however, to what extent cross-talk with GSH might affect the ability and affinity of TRX to bind and interact with its protein targets, or its subcellular localization. Nevertheless, perturbations in thiol redox status and changes in antioxidant pools have been observed in clinical and in experimental diabetes (18, 39), and diabetes has been shown to alter GSH metabolism by decreasing total GSH (26) or increasing GSSG (39) and the GSSG/GSH ratio (18) also in brain tissue (35). With respect to exercise training, increased (1, 16, 61) or unchanged (12, 20, 34) GSH and GSSG levels have been reported in brain tissue. Furthermore, induction of oxidative stress by physical exercise may regulate the signaling pathways through TRX system (21, 40, 71), possibly with involvement of the GSH system. The metabolism of GSH and TRX may also follow a tissue-specific pattern. Indeed, in accordance with the present study, Liu et al. (34) reported that GSH response in brain to exercise-induced oxidative stress was quite different from other tissues, with no significant response by exercise training. Moreover, Somani et al. (61) have pointed out that the activity of antioxidant enzymes and their response to exercise training may differ according to the brain region.

We found that experimental diabetes increased total GPX activity without affecting GPX1 protein levels or GRX mRNA and protein, whereas GRD activity decreased. GRD generates GSH from GSSG, and GPX works in concert with GSH in the decomposition of hydrogen peroxide or other organic hydroperoxides, resulting in the oxidation of GSH to GSSG. Similarly, GRX catalyzes the reduction of disulfide bonds in proteins, oxidizing GSH to GSSG. Hence, an increased GPX activity coupled with decreased GRD activity may explain the

### Table 1. Effect of 8 wk of exercise training on antioxidant enzyme activity and protein and mRNA levels in rat brain

<table>
<thead>
<tr>
<th></th>
<th>Nondiabetic Animals</th>
<th>Diabetic Animals</th>
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<tbody>
<tr>
<td></td>
<td>Untrained</td>
<td>Trained</td>
</tr>
<tr>
<td>TrxR1 activity, U·min⁻¹·mg protein⁻¹</td>
<td>7.86±0.35</td>
<td>8.42±0.39</td>
</tr>
<tr>
<td>TRX1 activity, U·min⁻¹·mg protein⁻¹</td>
<td>20.62±0.69</td>
<td>20.17±1.02</td>
</tr>
<tr>
<td>CAT activity, U·min⁻¹·mg protein⁻¹</td>
<td>0.43±0.05</td>
<td>0.40±0.01</td>
</tr>
<tr>
<td>GRX1 protein, AU</td>
<td>1.04±0.13</td>
<td>1.02±0.11</td>
</tr>
<tr>
<td>GRX1 mRNA, AU</td>
<td>1.08±0.18</td>
<td>1.09±0.19</td>
</tr>
<tr>
<td>CAT protein, AU</td>
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<tr>
<td>CAT mRNA, AU</td>
<td>1.30±0.27</td>
<td>1.10±0.41</td>
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Values are means ± SE. TrxR1, thioredoxin reductase-1; TRX1, thioredoxin-1; GRX1, glutaredoxin-1; CAT, catalase; AU, arbitrary units. No statistically significant differences were found.

Fig. 2. Effect of 8 wk of exercise training on the levels of total glutathione (TGSH), oxidized glutathione (GSSG), and GSSG/TGSH ratio in nondiabetic and diabetic rat brain. Values are means ± SE. Groups are as in Fig. 1. Two-way ANOVA for the difference due to SID: **P < 0.01, ***P < 0.001.
observed increased GSSG levels and GSSG/TGSH ratio in diabetic animals. On the other hand, TRX may replace GSH as the substrate for GPX (6). Therefore, induction of GPX activity may be a response to increased peroxidative stress in the diabetic state despite the depressed GRD activity. Previously, variable antioxidant enzyme responses to diabetes have been noted in brain tissue, with findings of either unchanged, increased, or decreased GPX and GRD (5, 30, 41, 68). Altogether these results indicate that antioxidant enzyme activity seems to vary from tissue to tissue, and the severity of diabetes may be a major contributing factor.

We also observed that experimental diabetes increased Cu,Zn-SOD protein in brain, without effect on total SOD activity or CAT. The published data on the effects of experimental diabetes on Cu,Zn-SOD or CAT activities in tissue have been very inconsistent (5, 23, 24, 44, 54) and are likely to be dependent on several factors, including differential baseline expression of these enzymes and techniques used to generate the diabetic animals. In our study, TRX1 correlated strongly with other antioxidant enzymes (mostly the SOD isoforms and CAT), which represent much of the overall antioxidant enzyme capacity. We also found variable correlations that appeared different between exercise-trained and nontrained groups, but we cannot conclude that exercise training specifically targets CAT or SOD in addition to TRX1. Mn-SOD can be induced by TRX, increasing the removal of highly reactive superoxide anions (14). Thus exercise training has the potential of increasing TRX1 levels in brain, which in turn may induce Mn-SOD. It is therefore possible that the cytoprotective effects of TRX1 could also be mediated in part through Mn-SOD.

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**Fig. 3.** Effect of 8 wk of exercise training on glutathione peroxidase-1 (GPX1) protein and total GPX activity, and glutathione reductase (GRD) activity in nondiabetic and diabetic rat brain. Values are means ± SE. Groups are as in Fig. 1. Two-way ANOVA for the difference due to SID: ***P < 0.001; due to training: ‡‡‡P < 0.001.

**Fig. 4.** Effect of 8 wk of exercise training on total superoxide dismutase (SOD) activity, Mn-SOD protein, and Cu,Zn-SOD protein and mRNA levels in nondiabetic and diabetic rat brain. Values are means ± SE. Groups are as in Fig. 1. Two-way ANOVA for the difference due to SID: *P < 0.05; due to training: ‡‡P < 0.01; and interaction between training and diabetes: # P < 0.05.
Furthermore, exercise training increased GPX activity in nondiabetic animals, but decreased GRD activity in both exercise-trained groups. GRD may therefore be more susceptible to inhibition due to the increased pro-oxidant tone by exercise. Nevertheless, the levels of Cu,Zn-SOD protein were slightly increased in all exercise-trained animals, but CAT mRNA, protein levels, and activity did not change. Only few studies are available on the effects of exercise training or acute exercise on antioxidant enzyme activities in the brain. Radak et al. (49) demonstrated that acute exercise does not significantly alter antioxidant enzyme status in brain, whereas Somani and Husain (59, 60) and Husain and Somani (25) found that exercise training differently altered CAT, GPX, GRD, and SOD activity in brain depending on the region investigated. On the other hand, acute exhaustive exercise did not affect SOD and GPX activities in hippocampus, prefrontal cortex and striatum (1).

In conclusion, our findings suggest that exercise training increases TRX1 protein in brain without a simultaneous rise in TXNip. Moreover, experimental diabetes seems to be associated with an incomplete TRX response to exercise training and an incomplete translation of TRX1 mRNA into protein. Because the beneficial effects of physical exercise on TRX system were affected by a diabetic state, our findings provide an interesting insight for further investigation. The response of key antioxidant enzymes to experimental diabetes and exercise training was variable in brain tissue. Although we did not find any direct association between TRX and glutathione responses, the increased GSSG/GSH ratio indicated increased oxidative stress, which may be a cause or a consequence of perturbed antioxidant enzyme defenses in experimental diabetes. Nevertheless, strategies to improve brain antioxidant status and redox regulation in a safe and physiological manner using physical exercise may provide a means for improving brain health.

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