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ORIGINAL ARTICLE

Short-term effect of low-, moderate-, and high-intensity exercise training on cerebral dopamine neurotrophic factor (CDNF) and oxidative stress biomarkers in brain male Wistar rats

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Abstract
Neurotrophic factors and exercise training are effective in the growth and survival of neuronal cells. These factors play a protective role against oxidative stress damage and have the same function as antioxidants. The purpose of this study was to investigate the effect of a session of endurance training with three different intensities on CDNF, SOD, and MDA levels of cerebral cortex in male rats. Thirty-two male Wistar rats (aged 20 weeks) were divided randomly into two control and training groups. The training group consisted of low-, moderate-, and high-intensity trainings. The training groups, after getting familiarization with the rodent treadmill, were dealt with an acute training session with three different intensities. The CDNF level of cerebral cortex was measured by ELISA assay, and the SOD and MDA levels of cerebral cortex by spectrophotometery. A significant difference was seen in the CDNF level between low- and high-intensity groups, as well as between high-intensity groups and control group ($P = 0.001$). The levels of SOD were increased significantly among all groups (except for control and low-intensity groups). The acute training with different intensities significantly prevents the increase in MDA level of cerebral cortex ($P = 0.005$). The result of this study shows that the physical exercise even in the short term can affect the protective factors and antioxidant system in neuronal cells. However, the benefits of high-intensity training were higher than others. Therefore, suggested that the role of acute exercise with different intensities should be carefully considered for the preconditioning against neuronal degenerative diseases.

Keywords Endurance training · CDNF · SOD · MAD

Abbreviation

CDNF	Cerebral dopamine neurotrophic factor
SOD	Superoxide dismutase
MAD	Malondialdehyde

Introduction

The benefits of exercise activity on brain tissue and secretion of neurotrophic factors in animal and human samples have been proven (Palasz et al. 2018; Shirvani et al. 2017). The physical exercise increases synaptic variability by directly affecting the synaptic structure and enhancing synaptic strength, as well as by strengthening the mechanisms associated with variability, including neurogenesis, metabolism, and vascular function (Dong et al. 2018). These structural and functional changes have been proven by the training in different regions of the brain, and have been well studied in the hippocampus (Abhijit et al. 2018). The main mechanism of mediating these broad benefits of the exercise training in the brain is the induction of central and peripheral growth factors and growth factor cascades that lead to structural and functional changes (Cotman et al. 2007). Neutrophic factors are secretory proteins that bind to their target receptors to prevent the reduction in the neuronal cells (Hellman et al. 2010). Cerebral dopamine neurotrophic factor (CDNF) is a newly detected neurotrophic agent with neurotrophic, neuroprotective, and neuroregenerative activities (Lotharius et al. 1999). The CDNF has the ability to protect the function of dopaminergic cells in mouse models of Parkinson's disease. Also, the CDNF

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protein can be useful in the treatment of Parkinson's disease (Lindholm and Saarma 2010). However, the mechanism of neuroprotection of the CDNF is not well defined (Hellman et al. 2010). The CDNF is a protein playing a major role not only in the survival of neurons, but also in the survival, proliferation, and differentiation of non-neuronal cells and tissues. The CDNF is distributed mainly in central nervous system cells including the hippocampus, cerebral cortex, midbrain, cerebellum, substantia nigra, and corpus striatum (Sun et al. 2011). Human studies suggested hippocampal atrophy with Parkinson's disease (Apostolova et al. 2012). The neurons of substantia nigra and corpus striatum are damaged in the Parkinson's disease, and hippocampus is the most vulnerable brain area to oxidative stress because of their high ability in neuronal variability.

Oxidative stress following the formation of free radicals is thought to play a major role in the neuropathology of the disease (Olanow 1990). The brain suffers from oxidative damage due to its higher metabolic rate, lipid content, and lower levels of antioxidant enzymes (Li and Wang 2013). Several oxidative stress brain markers and antioxidant enzymes have been used to evaluate brain damage. Although malondialdehyde (MAD) assay shows methodological limitations (Lefevre et al. 1998), it is the most common lipid peroxidation marker and it is still a widely used marker of oxidative stress. MAD can express in the heart, liver, and brain (Chirico et al. 2016). Among the antioxidant enzymes that are identified in the brain and are affected by exercise is superoxide dismutase (SOD). Studies have demonstrated that manganese superoxide dismutase (Mn-SOD), a primary cellular defense enzyme involved in protecting cells from oxidative stress (Chan 1996), is a direct target of STAT3 in ischemia reperfusion-induced neuronal cell death (Houston et al. 2009). It is well established that exercise plays an important preventive and therapeutic role on oxidative stress-associated brain diseases such as Parkinson (Mattson and Magnus 2006).

It has been shown that injection of 6-hydroxydopamine (6-OHDA) at a predetermined dosage in rats results in progressive and gradual loss of dopaminergic neurons in the substantia nigra whose trend is similar to the neuropathology of the Parkinson's disease and is considered as a valid empirical model for showing the stages of the onset of the disease (Gerlach and Riederer 1996). The neurotoxin 6-OHDA through producing free radicals, which in turn has cytotoxic effect, disrupts calcium homeostasis by increasing the penetration or exacerbation of release from intracellular reserves (Sautter et al. 1997), affecting the genetic regulation and induction of apoptosis (Lotharius et al. 1999) and causing neuronal death. For the last three decades, levodopa has been employed as the best medicine for Parkinson's treatment. Apart from the positive effects of this drug, its long-term usage results in side effects such as turbulence (excitement and stimulation), hallucinations, psychiatric problems, dyspareunia, and excessive sexuality (Rhodes et al. 2005), encouraging further search for better treatment and prevention methods for the disease.

Researchers has shown that there is a relationship between tremor and immobility (Stern 1993). In this regard, the training is important, and it is shown to prevent orthopedic problems associated with its primary symptoms (Wu et al. 2011). The training can change the level of neurotransmitter release, such as glutamate, dopamine, acetylcholine, and serotonin in the brain (Naderi et al. 2007). Evidence suggests that the training will activate the dopaminergic system of the brain and increase the dopamine present in corpus striatum. These findings increase the likelihood that the training reduces the vulnerability of dopaminergic neurons to 6-OHDA (Yoon et al. 2007). In this area, researchers have argued that the exercises increasingly enhance survival rate and resistance to brain damage and increase the nerve growth of the hippocampus (Johnson et al. 2003). Among the various training patterns, voluntary wheel running, compulsory treadmill run, and resilient muscular movement are the most commonly used training models. These trainings, apart from their physical benefits, improve cognitive function and facilitate neuroregeneration after brain damage. The training seems to be effective in improving brain function by balancing redox state, which increases resistance to oxidative stress and accelerates oxidative stress elimination (Radak et al. 2007). The training increases the survival of the nerve cells and facilitates the functioning of the brain after injury. Some concluded that overtraining fatigue can lead to the production of free radicals, while short-term submaximal training with 70% maximal oxygen consumption may reduce lipid peroxidation (Lovlin et al. 1987). In an overview article, regular training has reduced oxidative stress, and overtraining has increased the oxidative stress (Radak et al. 2008).

It is stated that injection of CDNF into corpus striatum can prevente the degeneration of neurons. In the only study regarding training and changes in the levels of CDNF, it has been shown that a long-term volunteer training activity increases the CDNF level of cerebral cortex in an experimental mice model of 6-OHDA (Fallah Mohammadi et al., under press). Apparently, volunteer training activities have a neuroprotective role in counteracting the 6-OHDA neurotoxicity, which is applied by the CDNF. Can the endurance training protect neurodegeneration from injectable toxins by increasing the CDNF levels in other parts of the brain? Therefore, due to the fact that the protective effects of endurance training with different intensities on the CDNF, SOD, and MDA levels of cerebral cortex in male rats have not been studied so far, the purpose of this study was to determine the impact of a session of endurance training

with three different intensities on CDNF, SOD, and MDA levels of cerebral cortex in male rats.

Materials and methods

The study animals

In this study, 32 male Wistar rats (aged 12 weeks) were obtained from the Pasteur Institute of Amol. The animals were transferred to a laboratory for 2 weeks in order to adapt to the new environment as groups of 4 rats in transparent polycarbonate cages at temperature of 20–24 °C and humidity of 45 to 55% and kept in 12:12-h light-dark cycle (Shirvani and Aslani 2017). During the research period, the animals had free access to food (pellete, Bahapparvar Co., Iran) and water (via special bottles).

The animal grouping

The rats after seven sessions of getting acquainted with the activity on the rodent treadmill were divided randomly into two main control and training groups. The training groups consisted of low-, moderate-, and high-intensity trainings. Since the weight of the animals was not exactly the same, they were weighed and classified in cages with a weight difference of 20 g to homogenize the subjects in terms of weight. Then, a mouse was selected randomly from each of the cages with a determined weight category and placed in the main groups. We tried to get the average weight between the different groups as close as possible. Accordingly, the mean weight of the rats in different groups after the study classification was 210 ± 7 g on average (Table 1).

Exercise protocol

The training groups (three groups with 24 rats in total), after getting acquainted with the rodent treadmill (Faculty of Physical Education, Mazandaran University) were dealt with an acute training session with three different intensities. The maximum stress failure criterion of the mice was the contact of each subject during the 2 min five times with shocker of the rodent treadmill (Table 2).

Table 1 Animal groups

Groups	Weight (g)	Number
Control (pre-test)	215.4 ± 1.60	8
Low-intensity training	214.7 ± 1.53	8
Moderate-intensity training	215.3 ± 1.01	8
High-intensity training	213.8 ± 1.82	8

Biopsy

At first, the mice were anesthetized by combining ketamine and xylazine at a ratio of 60 to 40 (Shirvani and Arabzadeh 2018). The mouse head was cut off with a special scissor; the whole brain was removed from the braincase and immediately placed in liquid nitrogen. The hippocampus was then dissected from other parts of the brain. The tissues were kept at − 80 °C. After homogenization with centrifugation, the CDNF levels of the groups were measured by a laboratory kit (CUSABIO, China). Coefficient of dispersion and sensitivity of this method are 0.039 ng/ml and 8%, respectively.

Measuring superoxide dismutase enzyme activity, protein, and malondialdehyde of cerebral cortex

The superoxide dismutase activity was measured by the spectrophotometry and the protein content using a conventional Bradford method based on the reference. The MDA level was measured based on the thiobarbituric acid (TBA) reaction at boiling point using the spectrophotometry according to the reference (Aslani et al. 2015).

Results

The changes in the weight of subjects in all groups are shown in Table 1. The results of this study showed that, there is a significant difference between the CDNF, SOD, and MDA levels of cerebral cortex after a session of endurance training with different intensities compare to control group ($P = 0.025$, $P = 0.006$, and $P = 0.0008$) (Figs. 1, 2 and 3). There is no significant difference between the CDNF and SOD levels of cerebral cortex in the low-intensity and control groups ($P = 0.28$ and $P = 0.22$, respectively). In addition, the mean of CDNF showed that, there is no significant difference between the low- and moderate-intensity groups ($P = 0.28$), as well as between the moderate- and high-intensity groups ($P = 0.28$) (Fig. 1). A significant difference was seen in the CDNF level between low- and high-intensity groups, as well as between high-intensity groups and control group ($P = 0.001$) (Fig. 1). Also, the levels of SOD were increased significantly among all groups (except for control and low-intensity groups) (Fig. 2). Among all groups, the training with different intensities significantly prevents the increase in MDA level of cerebral cortex (Fig. 3).

Discussion

This is the first study to investigate the effect of different intensities of training on CDNF, SOD, and MDA levels of cerebral cortex. The main finding of this study showed a

Table 2 Training protocol for animal

Groups	Training status	Number	Description
Control (pre-test)	–	8	The untrained group kept in the cage during the training period
Low-intensity training	Training	8	15 m/min for 30 min on the rodent treadmill
Moderate-intensity training	Training	8	25 m/min for 30 min on the rodent treadmill
High-intensity training	Training	8	12 m/min, followed by adding 3 m every 3 min to reach a final speed of 24 m/min

significant relationship between training and changes in CDNF, SOD, and MDA levels of cerebral cortex. The study results revealed that and increase in the training intensity significantly increased the CDNF and SOD levels and also prevented the increase in the MDA level. It can be said that the high-intensity training more than the low- and moderate-intensity trainings has been able to increase the CDNF levels of cerebral cortex. In this study, the CDNF and SOD levels showed a direct correlation with training intensity. No research has been done so far to investigate the effect of trainings with different intensities on the CDNF, SOD, and MDA levels of cerebral cortex. As a result, the findings of this study will be compared with studies that investigated the effects of training with different intensities and protocols in various tissues regarding the neurotrophic factors.

Studies on the effect of exercise on brain oxidative stress in rats have shown that moderate aerobic activity increases resistance to oxidative stress and reduces cellular damage (Chalimoniuk et al. 2015). These effects can greatly differ between various brain regions. The results of this study showed that acute endurance exercise increased the amount of SOD in the cerebral cortex in brain rat while amount of MAD has decreased. Various investigators have determined the effect of exercise on oxidative damage and/or the free radicals scavenging enzymes in the brain (Di Meo and Venditti 2001; Venditti and Di Meo 1996). Exercise training can increase antioxidant defenses in the brain (Sadowska-Krepa et al. 2013; Sadowska-Krępa et al. 2011). It was shown that moderate exercise from young ages may counteract the decline of some aging-associated detoxication processes in the brain; interestingly, at least some of these processes show considerable differences between various brain regions (Bayod et al. 2014). Aerobic exercise is known to elevate the activity of two constitutively expressed nitric oxide synthases (NOSs) in the brain that are postulated to exert a beneficial effect on brain function (Katusic and Austin 2013; Pietrelli et al. 2011). Both these enzymes can also contribute to brain lipid peroxidation due to NO reaction with the superoxide radical production and the resulting production of the peroxynitrite radical (Beckman 1994).

The exercise can increases the activity of the endogenous antioxidant system in the brain. It has been suggested that several factors, including genes, neurotransmitters, and neurotrophins, contribute to the useful effect of the training on the functions of the brain. The neurotrophins include nerve growth factor, basic fibroblast growth factor, insulin-like growth factor 1, brain-derived neurotrophic factor, and neurotrophic factor 3 to 7 play a key role in the survival, differentiation, communication, and formation of neurons (Van Praag 2008). Studies showed that the glial cell-line neurotrophic factor (GDNF) prevents dopamine depletion. This effect attributed the training's usefulness to increasing the amount of endogenous antioxidants and reducing the destructive degree of oxidative stress (Smith and Cass 2007). Increasing the antioxidant capacity through training occurs by increasing glutathione peroxidase, SOD, catalase, and heat shock protein. The training with increased expression of neurotrophins, including the GDNF, can lead to an improvement in intracellular

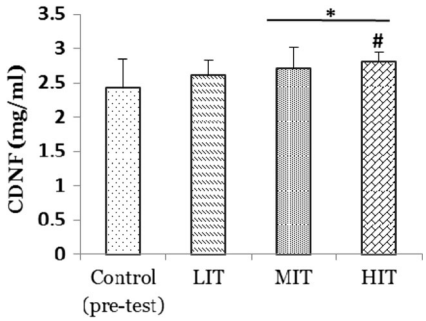

Fig 1 Levels of CDNF in cerebral cortex. LIT low-intensity training, MIT moderate-intensity training, HIT high-intensity training, *Significant difference with control group ($P = 0.001$); #Significant difference with low intensity group ($P = 0.05$)

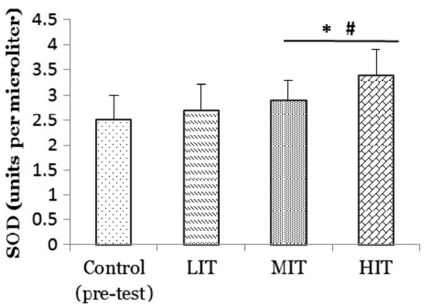

Fig 2 Levels of SOD in cerebral cortex. LIT low-intensity training, MIT moderate-intensity training, HIT high-intensity training, *Significant difference with control group ($P = 0.001$); #Significant difference with low intensity group ($P = 0.05$)

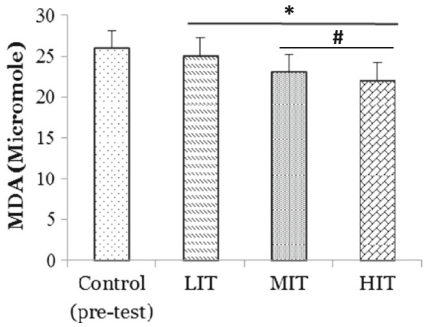

Fig 3 Levels of MAD in cerebral cortex. LIT low intensity-training, MIT moderate-intensity training, HIT high-intensity training, *Significant difference with control group ($P = 0.001$); #Significant difference with low intensity group ($P = 0.05$)

defense against ROS, thereby increasing the antioxidant capacity. The GDNF also prevents dopaminergic neuronal vulnerability and increasing dopamine secretion (Smith and Cass 2007). Reducing the destructive degree of oxidative stress occurs when training creates a moderate oxidative stress to prevent severe stress. This action happens by establishing compatibility. The findings of this study indicate that the endurance training affects brain mitochondria by the increase in antioxidant capacity and a reduction in the oxidative factors. Reducing these oxidative factors explains the increased protective factors of the brain (Swain et al. 2003). One of the profound effects of endurance training is to stimulate mitochondrial survival by increasing the number of mitochondria that is developed after a few weeks of training. This increase in the number of mitochondria causes high energy availability, the low production of ROS, and other beneficial processes that all play a neuroprotective role. Four weeks of voluntary training on treadmill by male and female mice showed an increase in density and function of mitochondria. These findings suggest that training through enhancing mitochondrial production is likely to be effective in preventing diseases associated with mitochondrial defects such as aging and degenerative disorders (Mabandla and Russell 2010). The findings from animal studies support the concept that the training may induce mechanisms regulating brain-derived neurotrophic factor (BDNF) that enhances neuronal variability that is another effective mechanism from training (Radak et al. 2007). It can be guessed that the mesencephalic astrocyte-derived neurotrophic factor (MANF) and CDNF may be activated as a result of stimulation of physiological damage. Although the CDNF and MANF affect dopaminergic and cortical neurons, more studies are needed to find out more about their effects on PNS neurons or other types of neurons in living organisms (Lindholm et al. 2007). As mentioned, the neurotrophins are important in the treatment of neurological diseases. The CDNF has been considered for its importance in the treatment of neuronal diseases such as Parkinson's disease. Today, drug therapy is used to treat Parkinson's disease. L-Dopa is used as the main drug for the treatment of Parkinsonian people. This medication has side effects; for example, the dopamine increases the frontal lobe of the brain. It also increases the level of stress-related hormone such as serum corticosterone (Carey et al. 1995). These two factors may be two major mental health concerns for Parkinson's patients. For this reason, researchers are trying to find better ways to cure. One of these strategies is the increase in neurotrophic factors. Parkinson's disease results in dopamine deficiency in the corpus striatum and indirectly in the cortical dysfunction. The increases in glutamate transfer in the basal ganglia are observed in Parkinson's disease and glutamate mediates excitotoxicity. It has been suggested that this agent may lead to the neurodegeneration. High concentrations of extracellular glutamate act as a neurotoxin and cause cellular damage and cell death in Parkinson's patients (Liguz-Lecznar and Skangiel-Kramska 2007). The BDNF regulates the release of glutamate from cortical neurons (Zhang et al. 2013). Recently, the CDNF is known as neurotrophin. The CDNF may be important, like the BDNF, to regulate the release of glutamate in the cerebral cortex. Several studies have been conducted on the effects of neurotrophins on nervous system diseases. In the studies on neuroprotective effects, it has been concluded that injection of 10 μg of CDNF into corpus striatum 6 h before injection of 6-OHDA into corpus striatum significantly reduced the rotational behavior by 2 and 4 h after intoxication. Also, the number of tyrosine hydroxylase-positive (TH-positive) dopaminergic cells in substantia nigra and tyrosine hydroxylase fibers-positive in corpus striatum was significantly higher in the rats exposed to the CDNF. It has been shown that the CDNF is a protein released into in vitro environment to save dopaminergic neurons from death. The neuroprotective effects of CDNF are dose-dependent, as 3 μg of the CDNF significantly reduced rotational behavior in Parkinsonian rats and increased the number of TH-positive cells in substantia nigra, which was lower than that of effect with 10 μg. The protective effects of CDNF were significantly lower at the dose of 1 μg (Lindholm et al. 2007). The studies on neuroregeneration indicated that the injection of 10 μg of CDNF into corpus striatum 4 weeks after injection of 6-OHDA into corpus striatum resulted in the recovery of functional activity of the dopaminergic system in corpus striatum-substantia nigra in adult rats. The implementation of training programs is one of these ways of increasing neurotrophins. Researchers have argued that physical activity has beneficial effects on brain health, including energy metabolism, synaptic variability, increased cognitive function-related proteins, and mitochondrial function. Training can also have a protective effect against several neurological diseases such as Parkinson's and Alzheimer's (Ferreira et al. 2011). Several studies have been conducted on the effects of training on neurotrophic factors. For example, in a study conducted by Mirzai et al., the effects of three training periods of 30, 60, and 90 min on treadmill for 8 weeks were investigated on changes

in the hippocampus BDNF. Study of the levels of hippocampal BDNF in training groups of 30, 60, and 90 min showed that the levels of hippocampus BDNF were significantly increased in the 60-min training group compared to the 30-min training group, sham group, and control. The levels of hippocampal BDNF in the 90-min training group were significantly increased compared to sham and control groups. As we know, severity and duration have a direct impact on the protective responses. It has also been shown that the training intensity on neurogenesis and the expression of BDNF mRNA and N-methyl-D-aspartate receptor type 1 (NMDAR1), vascular endothelial growth factor (VEGF), and fetal liver kinase-1 (FLK-1) in the hippocampus of rat aged 5 weeks. Hence, the intensity is the effective factor on the expression of neurotrophins (Lou et al. 2008). The neuroprotective property of CDNF is similar to the GDNF (Lindholm et al. 2007). The GDNF is affected by physical activity and is increased by training, so it can be assumed that the training has an upregulatory property for GDNF (Cohen et al. 2003). In a study conducted by Sakner in 2012, passive training increased the GDNF (Sackner 2012). The mechanism of action of the CDNF may be similar to that of the GDNF. There are three important mechanisms in place for the training effect on the brain of Parkinson's patients: one of these mechanisms is the GDNF that is a factor in the survival of neurons and the morphological differentiation of dopaminergic neurons. This factor binds to the cell surface and activates the tyrosine kinase signal (Al-Jarrah 2013). Following the activation of tyrosine kinase, a number of intracellular signaling pathways stimulate cell growth and survival, including Ras and mitogen-activated protein kinase (MAPK or MAP kinase) (Berchtold et al. 2005). Another possible mechanism for GDNF action is that GDNF rescue dopamine-producing neurons from cell death with upregulation of antioxidant enzymes such as glutathione peroxidase, superoxide dismutase, and catalase. The mechanism of action of the CDNF may be similar to that of the GDNF. The reason for a significant increase in CDNF in a high-intensity training group may be the presence of oxidative stress that occurs by high-intensity training compared to the low-and moderate-intensity training groups. Recent studies have shown that the CDNF and its equivalent of MANF against endoplasmic reticulum (ER) stress exhibit cellular protective property. Extreme ER stress leads to activation of apoptosis signaling and the CDNF prevents this action. The crystal structure of C-terminal MANF and CDNF supports the theory that it can act as a protective protein against ER stress and subsequently cell death. As stated, the dopaminergic neurons are degenerated in the Parkinson's disease (Lindholm et al. 2007). The MANF level was increased in the brain of adult rats after developing pathological and harmful conditions such as ischemia, indicating regulation of neuronal survival and synaptic variability (Lindholm et al. 2007).

In conclusion, the present study indicated that the CDNF and SOD levels were significantly increased in the moderate-intensity training higher than in the low-intensity training as well as in high-intensity training more than in the moderate intensity. In addition, training with different intensities prevented the increase in MDA level. Therefore, high-intensity exercise training pattern can be used to prevent neurodegenerative diseases such as Parkinson's disease. It is suggested that the role of acute exercise with different intensity, duration, and frequency should be carefully considered for the prevention and treatment of neuronal degenerative diseases.

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Compliance with ethical standards

This study was conducted according to the Declaration of Helsinki guidelines and approved by the Ethical Committee of Mazandaran University (Ethical cod #IR.BMSU.REC.1395.987).

Conflict of interest The authors declare that they have no conflict of interest.

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