Exercise and DHA Prevent the Negative Effects of Hypoxia on EEG and Nerve Conduction Velocity

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Abstract

Erken, Haydar Ali, Gülten Erken, Rıdvan Çolak, Osman Genç. Exercise and DHA prevent the negative effects of hypoxia on EEG and nerve conduction velocity. *High Alt Med Biol* 14:360–366, 2013.—It is known that hypoxia has a negative effect on nervous system functions, but exercise and DHA (docosahexaenoic acid) have positive effect. In this study, it was investigated whether exercise and/or DHA can prevent the effects of hypoxia on EEG and nerve conduction velocity (NCV). 35 adult Wistar albino male rats were divided into five groups ($n=7$): control (C), hypoxia (H), hypoxia and exercise (HE), hypoxia and DHA (HD), and hypoxia and exercise and DHA (HED) groups. During the 28-day hypoxia exposure, the HE and HED groups of rats were exercised (0% incline, 30 m/min speed, 20 min/day, 5 days a week). In addition, DHA (36 mg/kg/day) was given by oral gavage to rats in the HD and HED groups. While EEG records were taken before and after the experimental period, NCV records were taken after the experimental period from anesthetized rats. Data were analyzed by paired *t*-test, one-way ANOVA, and post hoc Tukey test. In this study, it was shown that exposure to hypoxia decreased theta activity and NCV, but exercise and DHA reduced the delta activity, while theta, alpha, beta activities, and NCV were increased. These results have shown that the effects of hypoxia exposure on EEG and NCV can be prevented by exercise and/or DHA.

Introduction

STAYING AT HIGHER ALTITUDES in order to have better exercise performances than at sea level, training athletes (Wilber, 2007), skiers (Mizuno et al., 1990), high-altitude climbing athletes (Schoene et al., 1984), and many other athletes are exposed to hypoxia.

The brain is extremely sensitive to hypoxia since its glycolytic capacity is low (Erecinska and Silver, 1989, 1994; Siesjö, 1978). Previous studies showed that hypoxia has negative effects on the brain and nervous system functions (Gruss et al., 2006; Krnjevic, 1999; Simonova et al., 2003). On the contrary, positive effects of physical exercise and docosahexaenoic acid (DHA) on the central and peripheral nervous system (PNS) functions have been reported (Balducci et al., 2006; Coste et al., 2003; Fontani et al., 2007; Kashihara et al., 2009; Wurtman et al., 2006). While EEG is an important indicator showing central nervous system functions, nerve conduction velocity (NCV) is a parameter that shows the PNS functions. In some previous studies, it was demonstrated that hypoxia increased the delta and theta activities (Kraaier et al., 1988; Saletu et al., 1990), but it reduced alpha activity (Kraaier et al.,

1988; Saletu et al., 1990) and NCV (Carrington et al., 1994). In another study, it was reported that hypoxia reduced theta activity (Budzinska and Ilasz, 2007). In other studies, it was shown that, unlike hypoxia, exercise and DHA reduced the delta activity and increased alpha and beta activities (Crawford, 2006; Li et al., 2008; Takeuchi et al., 2002; Youngstedt et al., 1993) and NCV (Balducci et al., 2006; Coste et al., 2003). Exercise and/or DHA can be suggested to prevent either partially or completely the effects of hypoxia on nervous system functions. The aim of this study was to investigate whether the negative effects of hypoxia on EEG and NCV can be prevented by exercise and/or DHA. For this, the EEG and NCV were tested. Also, moderate hypoxia was applied chronically to rats in this study, because altitude training was performed in moderate chronic hypoxia in previous studies (Geiser et al., 2001; Hahn and Gore, 2001; Saunders et al., 2009).

Materials and Methods

All experimental protocols conducted on animals were consistent with the National Institutes of Health Guidelines

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for the Care and Use of Laboratory Animals (NIH Publication No. 85-23) and approved by the Pamukkale University Ethics Committee of Animal Care and Usage. In the study, 35 adult Wistar Albino male rats were used (weighing 210 ± 18 g). Before the experiment, the rats were housed in a room with controlled temperature ($23 \pm 1^\circ\text{C}$) and relative humidity ($50 \pm 5\%$), and they were kept in transparent plastic cages ($42 \times 26 \times 15$ cm), each containing 3 to 4 rats, exposed to a 12:12 light/dark cycle. The food and water intake of the rats was not limited. The rats were randomly divided into five groups ($n=7$): control (C), hypoxia (H), hypoxia and exercise (HE), hypoxia and DHA (HD), and hypoxia and exercise and DHA (HED) groups.

Experimental protocol

Handling was applied to all rats for a week. EEG recordings were then taken from a group every day. After taking the EEG records, a 1-week waiting period was given for the scalp to heal. After the 1-week healing period, training exercise (10 m/min speed, 0% slope, 10 min/day) was applied by treadmill (MAY-TME 9805, Commat Co., Turkey) to HE and HED group rats at the same time (between 9:00–11:00 AM) every day in a week. After the 1-week training exercise period, all rats except group C were put in a hypoxic tent as one group each day. In addition to the experimental groups, four rats of the same breed and age were placed in the hypoxic tent for arterial blood gas analysis. Arterial Po_2 was measured from a rat every week. During the 28-day hypoxia exposure, the HE and HED groups of rats were exercised (30 m/min speed, 0% slope, 20 min/day, 5 days in a week). Exercises were performed in the same order and at the same time every day (between 9:00–11:00 AM). In addition, 36 mg/kg dose of DHA (cis-4,7,10,13,16,19-docosahexaenoic acid, Sigma-Aldrich Co., St. Louis, MO) dissolved in 1 mL corn oil (Yonca Co., Turkey) was given by oral gavage to the HD and HED groups of rats. The same amount of solvent was given to the H and HE groups every day by oral gavage. The control group was housed under standard laboratory conditions as mentioned above during the experimental period and the solvent was given by oral gavage every day for 28 days. At the end of the experimental period for 28 days, the rats were removed from the hypoxic tent as one group each day. Then EEG and NCV were recorded (Table 1).

Exposure to hypoxia

O_2 level in the environment was set to be 14% by using a hypoxic tent and oxygen generator (8850 SUMMIT 3in 1, Altitude Tech. Co., Canada). In order to reduce the CO_2

concentration in the internal environment, a CO_2 filter (Altitude Tech. Co.) was placed in the tent. Indoor air was observed continuously by O_2 (IBRID MX6, Industrial Scientific Co., USA) and CO_2 detectors (Testo 435, Testo AG, Germany). The O_2 level in the internal environment was maintained at the same levels by continuously monitoring it. Between 9:00 AM and 11:00 AM, when the tent door was opened for various interventions (such as exercise, providing food and water, etc.), the O_2 level increased to 16–17%. Approximately 30 min after closing the door, the O_2 level returned to 14% again. The CO_2 level was observed to vary between 300–2500 ppm during the experimental period.

Analysis of arterial Po_2

To confirm the effects of our moderate hypoxia system, the animals' arterial blood Po_2 values were measured once a week for 4 weeks during the experimental period. At the end of the first, second, third, and fourth weeks of the experimental period, one animal was anesthetized with a ketamin/xylazin cocktail (90 mg/kg and 10 mg/kg, respectively) and the left common carotid artery was surgically exposed. Arterial blood samples (0.2 mL) were obtained with an injector containing heparinized saline (20 IU/mL) for blood gas analysis. These processes were performed in a hypoxic tent. The samples were transported in a cold water bath (0°C), and were analyzed within 15 min using an ABL5 blood gas analyzer (Radiometer, Denmark). All animals were euthanized with an intraperitoneal injection of a high dose of ketamin/xylazin immediately after the measurement.

EEG and NCV recordings

Animals were anesthetized with ketamine/xylazine (Alfamine 10%, Ege Vet. Co., Turkey/Basilazin 2%, aniMedica GmbH, Germany; 75 mg/kg and 10 mg/kg, respectively, i.p.) and their heads were shaved. Their heads were then disinfected with batticon (Batticon, Adeka Co., Turkey) and incised from mid-frontal to mid-occipital. For a bipolar EEG recording, one of the AgCl electrodes was placed to the right parietal area, the other was placed to the mid-occipital area, and the ground electrode were placed to the tails of the rats by using EEG paste (Ten20, Weaver and Co., Colorado, USA). EEG was recorded by the PowerLab 8/SP data acquisition system and Chart 5 program (ADInstruments Co., Australia). The recording parameters were as follows: 0.3–50 Hz low and high frequency filter and 50 Hz notch filter. After EEG recording, the right sciatic nerves of all rats were removed and put into Ringer's solution. Later, nerve fibers were placed into the nerve chamber and NCV was recorded by electrical stimula-

TABLE 1. EXPERIMENTAL PROTOCOL FOR 51 DAYS

Handling (7 days)	EEG recording (1 day)	Healing (7 days)	Training (7 days)	Exposure to hypoxia and exercise; DHA or solvent gavage (28 days)	EEG and NCV recording (1 day)
All groups	All groups	All groups	HE and HED groups	All experimental groups except the control group. In addition to the experimental groups, four rats were placed in the hypoxic tent for blood gas analysis.	All groups

C, control; EEG, electroencephalography; HE, hypoxia and exercise; HED, hypoxia and exercise and docosahexaenoic acid; NCV, nerve conduction velocity.

TABLE 2. THE RELATIVE POWER VALUES (PERCENTAGE OF TOTAL EEG ACTIVITY) OF EEG FREQUENCY BANDS AND NERVE CONDUCTION VELOCITY VALUES OF RATS IN ALL EXPERIMENTAL GROUPS

	Delta (%)	Theta (%)	Alpha (%)	Beta (%)	NCV (m/sec)
C	64.10±9.32	18.55±1.92	12.97±2.58	4.35±1.07	33.95±1.68
H	66.92±11.65	12.14±2.43	14.22±1.51	6.69±2.32	30.16±1.92
HE	48.96±9.18	21.38±2.86	20.29±2.72	8.04±1.86	35.49±1.77
HD	52.72±5.64	20.01±1.55	19.58±2.13	7.84±1.35	36.83±2.41
HED	45.78±7.23	24.70±2.01	21.42±2.39	8.37±1.29	37.90±1.75

Data are presented as mean±S.D.; C, control; H, hypoxia; HD, hypoxia and docosahexaenoic acid; HED, hypoxia and exercise and docosahexaenoic acid; HE, hypoxia and exercise; NCV, nerve conduction velocity.

tion of nerve (10 V, 0.15 sec) for ten times in one second intervals.

Analyses

Thirty second artifact-free epochs were chosen from the EEG recordings of every rat and frequency analysis was performed using the Chart 5 program. The power spectra values for each frequency band were computed as the percentage of total power (Delta, 1–3.9; theta, 4–7.9, alpha, 8–12.9, beta 13–30 Hz). The average value of NCV taken from each rat was the defined NCV value of that rat. Statistical analyses were performed by transferring the data obtained from EEG and NCV into the SPSS 10.0 program. EEG frequency bands and NCV values of experimental groups were compared using One-way ANOVA and Post Hoc Tukey tests. Paired *t*-test was used to compare EEG frequency band activity before and after hypoxia protocol of each group. All results are

expressed as mean±S.D; $p < 0.05$ values were considered as statistically significant.

Results

EEG findings

No significant differences were found among the groups in any EEG frequency band before the experimental protocol.

The delta activity of groups HE, HD, and HED were decreased compared to the delta activity of the same groups before the hypoxia protocol ($p < 0.01$, $p < 0.05$; $p < 0.001$, respectively). Also, the delta activity of groups HE, HD, and HED were lower than groups C and H. (Differences from group C: $p < 0.001$, $p < 0.001$, $p < 0.001$, respectively; differences from group H: $p < 0.001$, $p < 0.001$, $p < 0.001$, respectively) (Table 2, Fig. 1).

The theta activity of group HED increased and the theta activity of group H decreased compared to the initial values of

FIG. 1. Changes in relative power (percentage of total EEG activity) of EEG frequency bands of rats in all experimental groups (Data are presented as mean±S.D.; C, control; H, hypoxia; HD, hypoxia and docosahexaenoic acid; HE, hypoxia and exercise; HED, hypoxia and exercise and docosahexaenoic acid). (A) Changes in relative power of delta frequency activity, * $p < 0.001$ versus C; † $p < 0.001$ versus H. (B) Changes in relative power of theta frequency activity, * $p < 0.01$ versus C; † $p < 0.001$ versus H. (C) Changes in relative power of alpha frequency activity, * $p < 0.001$ versus C; † $p < 0.01$ versus H. (D) Changes in relative power of beta frequency activity, * $p < 0.01$ versus C.

FIG. 2. Changes in nerve conduction velocity of rats in all experimental groups (Data are presented as mean $\pm$ S.D.; C, control; H, hypoxia; HD, hypoxia and docosahexaenoic acid; HE, hypoxia and exercise; HED, hypoxia and exercise and docosahexaenoic acid), * $p < 0.05$ versus C; ** $p < 0.01$ versus C; † $p < 0.01$ versus H; †† $p < 0.001$ versus H; # $p < 0.05$ versus HE.

the same groups ($p < 0.01$, $p < 0.01$, respectively). Also, the theta activity of group H was lower than group C ($p < 0.01$). The theta activities of groups HE and HD were higher than group H ($p < 0.001$, $p < 0.001$, respectively), and the theta activity of group HED was higher than groups C and H ($p < 0.01$, $p < 0.001$, respectively) (Table 2, Fig. 1).

The alpha activity of groups HE, HD, and HED increased after the experiment compared to the previous values ($p < 0.001$, $p < 0.001$, $p < 0.001$, respectively). Also, the alpha activity of groups HE, HD, and HED were higher than groups C and H (differences from group C: $p < 0.001$, $p < 0.001$, $p < 0.001$, respectively; differences from group H: $p < 0.01$, $p < 0.01$, respectively) (Table 2, Fig. 1).

The beta activity of groups HE, HD, and HED increased after the experiment compared to the previous values ($p < 0.01$, $p < 0.01$, $p < 0.01$, respectively). Also, the beta activity of groups HE, HD, and HED were higher than group C ($p < 0.01$, $p < 0.01$, $p < 0.01$, respectively) (Table 2, Fig. 1).

NCV findings

The NCV values of group H were lower than group C ($p < 0.01$). The NCV values of groups HE, HD, and HED were higher than groups C and H (differences from group C: $p < 0.05$, $p < 0.05$, $p < 0.01$, respectively; differences from group H: $p < 0.01$, $p < 0.01$, $p < 0.001$, respectively). In addition, the NCV value of group HED was higher than group HE ($p < 0.05$) (Table 2, Fig. 2).

There was no significant difference in amplitude of compound action potentials among the experimental groups.

Arterial PO_2 findings

In the arterial blood PO_2 analysis of the rats, PO_2 values were measured as 55, 56, 56, and 55 mmHg (first, second, third, and fourth weeks, respectively).

Discussion

In the present study, it was shown that hypoxia reduced the EEG theta activity and NCV. On the other hand, exercise and DHA reduced the delta activity and increased the theta, alpha, and beta activity and NCV. Another important point in our results is that the changes in EEG findings for groups H, HE, HD, and HED compared to the control group and the initial

values of the same groups were consistent. This result shows that the findings of this study were not caused by the individual differences between rats.

EEG waves

In our study, hypoxia exposure did not cause a significant increase in delta activity compared to control group. In contrast to our results, some previous studies showed that hypoxia caused an increase in delta activity (Burykh, 2005; Kraaier et al., 1988; Ozaki et al., 1995; Saletu et al., 1990; Schellart and Reits, 2001). The reason for this contradiction may be a few methodological differences among the studies. First, severe and acute hypoxia exposure was applied in previous studies (Burykh, 2005; Kraaier et al., 1988; Ozaki et al., 1995; Saletu et al., 1990; Schellart and Reits, 2001). In our study, PO_2 values were measured as 55–56 mmHg. Calder et al. (1997) classified 40–60 mmHg values for PO_2 as moderate hypoxia. According to this, the hypoxia exposure is moderate and chronic in our study.

Second, Saletu et al. (1990) showed that a permanent effect occurred in the central nervous system by hypoxia at the altitude of 6000 m (19,685 ft) and there was no permanent effect at lower altitudes. In our study, the hypoxia level approximately corresponds to 3400 m (11,154 ft). Therefore, in our study hypoxia possibly caused temporary effect on EEG delta activity.

Third, EEG was recorded during or immediately after the hypoxia exposure in previous studies (Burykh, 2005; Kraaier et al., 1988; Saletu et al., 1990; Schellart and Reits, 2001). However, in our study, EEG records were taken before and after the 28-day experimental period.

In the current study, exercise and DHA decreased delta activity. Similarly, previous studies reported that exercise (Li et al., 2008; Youngstedt et al., 1993) and DHA (Crawford, 2006; Takeuchi et al., 2002) decreased delta activity. Also, in our results, delta activity was found to be high in all groups. A possible cause for this was that EEG recordings were taken under general anesthesia in our experiments. Musizza et al. (2007) demonstrated that delta activity increases during deep general anesthesia.

In this study, hypoxia exposure decreased theta activity compared to the control group. In accordance with this, Budzinska and Ilasz (2007) reported that hypoxia reduced theta activity. On the other hand, exercise and DHA increased theta activity compared to the hypoxia group. Similarly, many previous studies reported that exercise and DHA increased the theta activity (Crabbe and Dishman, 2004; Fontani et al., 2007; Li et al., 2008). In the present study, the theta activity of group HED, with exercise and DHA applied together, was increased compared to the control and hypoxia groups. It is especially significant that the theta activity of group HED is higher than control group, showing that despite the hypoxia exposure this increase occurred.

In previous studies, theta activity was related to alertness (Grigg-Damberger et al., 2007), attention (Sauseng et al., 2007), perception (Başar et al., 2006), and cognitive functions such as memory (Klimesch, 1999; Onton et al., 2005). Also, recently it was shown that regular physical exercise and DHA develops memory and cognitive functions (Colcombe and Kramer, 2003; Fontani et al., 2007; Hillman et al., 2002; Lee et al., 2012; Narendran et al., 2012). Based on results of previous studies and our EEG findings, it could be suggested that

the negative effects of hypoxia on cognitive functions can be prevented by exercise and/or DHA.

In the current study, exercise and DHA increased alpha and beta activities. Similarly, in previous studies it was shown that exercise (Youngstedt et al., 1993) and DHA (Crawford 2006; Takeuchi et al., 2002) increased alpha and beta activities. While an increase in alpha activity is related to alertness (Nerad and Bilkey, 2005), vigilance (Olbrich et al., 2009), and semantic memory in humans (Klimesch, 1999), increase in beta activity is related to alertness (Nerad and Bilkey, 2005), attention (Makeig and Jung, 1995), emotion (Cole and Ray, 1985), anger (Rusalova et al., 2003), and sensorimotor cortex (Parkes et al., 2005) activities.

In the light of these findings, it can be said that although there are negative effects of hypoxic environment, exercise and/or DHA might have positive effects on cognitive functions such as attention and memory. Therefore, regular exercise and/or the supplement of DHA to diet can be recommended to individuals who are exposed to hypoxia (climbers, athletes, pilots, etc.).

Nerve conduction velocity

No significant differences were found among the experimental groups in amplitude values of compound action potentials. This finding points out that hypoxia exposure and other processes in our experiments have not been caused by dramatic axonal damage. However, hypoxia exposure decreased the NCV in this study. Similarly, Dousset et al. reported that hypoxia decreased the NCV (2001). Also, another study has shown that ATP levels decrease in peripheral nerves exposed to hypoxia (Brismar, 1981). Therefore, in hypoxia, metabolic energy required for the maintenance of membrane potentials and ionic homeostasis is consumed (Ritchie, 1985). The reason for the decrease in NCV in our results may be the decrease in ATP level and activity of ion pumps by hypoxia. Also, previous studies demonstrated that hypoxia hyperpolarized the cell membranes (Erdemli et al., 1998; Fujimura et al., 1997; Yamamoto et al., 1997). Hyperpolarization in neural membranes by hypoxia may be a factor for delaying the formation of action potential. Therefore, NCV can be reduced by hypoxia in our study.

In this study, the NCV value of the exercise group was higher than the control and hypoxia groups. Similarly, Balducci et al. (2006) showed that exercise caused an increase in NCV. Also, Howarth et al. (2010) demonstrated that exercise increased the inward current of Na^+ and Ca^{2+} . The possible reason of the increase in NCV may be the increased inward current of these ions.

In our study, similar to exercise, DHA increased the NCV. Similarly, it was shown that DHA increased the NCV in diabetic rats (Dines et al., 1993; Gerbi et al., 1998; Jarrahi et al., 1999). In other studies, it was reported that DHA taken with diet increases the NCV and prevents diabetic neuropathy in streptozotocin-induced diabetic rats by increasing DHA level in the membrane of the sciatic nerve (Coste et al., 2003; Pitel et al., 2007). In addition, Martinez and Vazquez showed that DHA contributes to myelination (1998). Furthermore, DHA increases the activities of transmembrane proteins like Na^+/K^+ -ATPase (Gerbi et al., 1998).

In this study, the NCV value of group HED was higher than groups C, H, and HE, but there were no significant differences between groups HED and HD. This finding showed that

DHA is more effective than exercise on NCV. Therefore, when supplementing the diet with DHA and/or exercise, DHA can be especially recommended to individuals who are healthy, exposed to nerve damage (e.g., diabetic neuropathy), and exposed to hypoxic conditions.

Conclusion

Negative effects of hypoxia on EEG and NCV can be prevented by exercise and/or DHA in rats. Even though exercise and DHA have a positive effect on both EEG and NCV, the effect of exercise is higher than DHA on EEG, while the effects of DHA are higher than exercise on the NCV in the current study.

Acknowledgments

The authors thank to Mrs. Zuhul Güçlü and Mr. Barbaros Şahin for their technical support.

Author Disclosure Statement

The authors declare that there is no conflict of interest. This study was supported by Pamukkale University Research Fund (2009SBE001).

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Received December 18, 2012;
 accepted in final form August 20, 2013.