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Repeated administration of vitamin E decreases 5HIAA levels producing antidepressant effect and enhance behavioural effects

Tahira Parveen, Beenish Nazi, Naila Amin and Darakhshan J. Haleem*
Departement of Biochemistry, Neurochemistry and Biochemical Neuropharmacology Research Unit, University of Karachi, Karachi, Pakistan

Abstract: Antioxidant act as a free radical scavengers. Vitamin E is well known antioxidant. This study was designed to investigate the behavioural effects following long term administration of Vitamin E. After four weeks administration of antioxidant, behavioural effects of rats were significantly enhanced. Behavioural effects monitored in present study are anxiety, depression, exploratory activity, learning and memory (short term and long term). Elevated plus maze, Swim test activity, open field and morris water maze respectively are used to observe the behavioural effects. Result shows that oral administration of vitamin E significantly increases no. of square crossing in open field and decrease latency period. Time spent in open arm and no. of entries in open arm increases significantly in elevated plus maze. In present study when animal is placed in morris water model controls take less time to reach platform hidden in opaque water. Immobilize time also decreases in swim test. All these results suggest that long term administration of antioxidant enhance behavioural effects.

Keywords: Vitamin E, antidepressant, 5-HT, 5HIAA, behavioural effects.
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***Author for Correspondence:** tahiraparveen@uok.edu.pk

INTODUCTION

Vitamin E is a major lipid soluble chain breaking antioxidant[1-3]. In normal functioning antioxidant in the system act as free radical scavengers[4-6.] Repeated administration of high doses of vit E improves neurological performance and brain mitochondrial function in aging mice[7.] Vitamin E is useful in the treatment of the pain[8,9], depression[10], eating disorder[11] and suppresses the oxidant damage of membranes[12]. Studies show that neurological disorders can be treated with antioxidant[13,14].

High Vitamin E doses improves survival[15], neurological performance and brain mitochondrial function in aging mice[16] . A severe deficiency of antioxidant is associated with neurological syndrome with typical clinical, neuropathlogical and electrophysiological abnormalities in both humans and experimental animals[17].

Vitamin E has the role of antioxidant in the treatment of neurodegenerative disorder[18] . The beneficial effects of Vitamin E supplementation on biochemical and kinetic properties of glycoprotein in hypertensive patients has been reported[19]. The antioxidant Vitamin E is a potent nutrient against coronary heart disease in women[20] and men[21]. It is reported previously that dietary Vitamin E deficiency produces anxiety[22].

In view of these finding present study is design to investigate the neurochemical and behavioural effects of long term administration of Vitamin E in rats.

MATERIAL AND METHODS

Animals

Twelve locally breed white albino Wister rats weighing about 150-250g (purchased from HEJ Research Institute of Chemistry, University of Karachi) were caged individually in pacifically designed cages in a quite room with free access to water and cubes of standard rat food for at least 1 week before starting the experiment.

Experimental procedure

Animals were divided into control and test. To test animals, the Vitamin E at a dose of 0.3 ml/day was given orally, daily for four weeks. The control animals were only given tap water.

After four weeks of repeated administration of drug, the activities of animals were monitored in different behavioural test.

Behavioural procedures

Open-field testing

The activity of control and Vitamin E treated rats were monitored in an open field apparatus. Open field is the square area of 76x76 cm with opaque walls of 42 cm height. The floor was divided by lines into 25 equal squares. The test was performed in a quiet room under white light to avoid any noise effect as described[23,24]. Animals were placed in the center square of the open field (one at a time). Activity in open field was determined by monitoring latency period and counting number of squares crossed for five minutes as described earlier [24]. Activities of control rats and drug treated rats were monitored in a balance design to avoid order effect.

Morris water maze test

The effects on spatial memory were examined by assessing performance in a Water Maze (WM) test designed in our laboratory. Actual Morris Water Maze is circular while we used rectangular maze that has been used before[25]. The method is not same as that described by them. It is a modification of their method. Dimensions of the WM are same as described by them. The WM apparatus used in the present study consisted of a transparent rectangular glass tank (60x30cms) filled with room temperature-water open field with powder milk, to the depth of 12cm. A wooden platform (15x13cm) was hidden 2cm below the surface of water in a fixed location. The experiment was performed after 30 minutes of injections. Initially the rats were trained and during the training session each rat was placed into the water facing the wall of the tank and allowed 120 seconds to locate and climb onto the submerged platform. The rat was allowed to stay on the platform for 10 seconds. If it failed to find the platform within the allowed time it was guided gently onto the platform. Memory functions of rats were tested by recording the retention latency (RL; the time taken by each rat to locate the hidden platform 24h after training). The cut off time for each session was 2 minutes.

Elevated plus maze test

The anxiolytic activity of drug in elevated plus maze model was measured according to method as previously reported [26]. Plus maze apparatus consist of four equal size arms. The two opposite arms are open while two were closed. The length of each arm was 50 cm and width is 10 cm. Arms were joined by the central area of 5 cm2. The length of the wall of the closed arm was 40 cm. The maze was elevated from ground at a height of 60 cm. To determine activity a rat was placed in the center of the plus maze and the time spent in the open arm was monitored for 5 minutes.

Forced swim test

Assessment of depressive symptoms was monitored by FST following 4 weeks of oral administration of drug. FST was performed as described by [27] [28]. To monitor the antidepressent activity rats are placed individually in a tank (53,19,28 cm). The water is filled upto 18cm. The height of the water is such in which animal is supposed to swim. Animal is subjected in the container for 5 minutes and behavioral scoring was performed by noting immobility time. After each test, rats were dried with towel and placed in home cage.

HPLC analysis

At the end of experiment animals were decapitated using guillotine. Brain was removed immediately and stored in –70°C for the determination of 5HIAA. By HPLC-EC as described earlier[29].

Statistical Analysis

The statistical analysis of results was performed by using Student`s t-test. P>0.05 were considered as non-significant.

RESULTS

Effects of vitamin E on exploratory activity

Open field activity is used to assess exploratory activity. Vitamin E enhances exploratory activity. Vitamin E treated rats significantly ($p<0.01$) decreased latency period and significantly ($p<0.05$) increased no. of squares crossed (Figure 1).

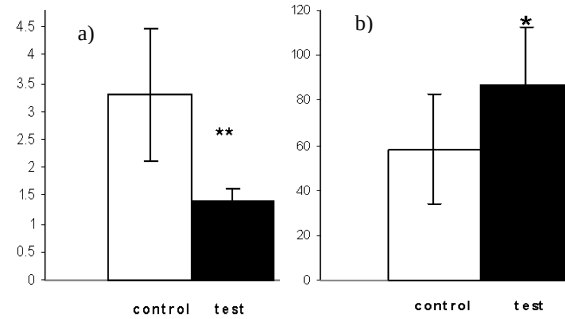

Figure 1: Effect of Vitamin E (0.3ml/day for four weeks) a) on latency period b) on number of squared crossed in open field activity. Values are mean±SEM, (n=6) significant difference by student t-test **($p<0.01$), *($p<0.05$) from water treated controls.

Effects of vitamin E on anxiety

Elevated plus maze is used to assessed anxiety. Anxiolytic effect is produced by Vitamin E. Vitamin E treated rats significantly ($p<0.01$) increased time spent in open arm and significantly ($p<0.05$) increase no. of entries in open arm (Figure 2).

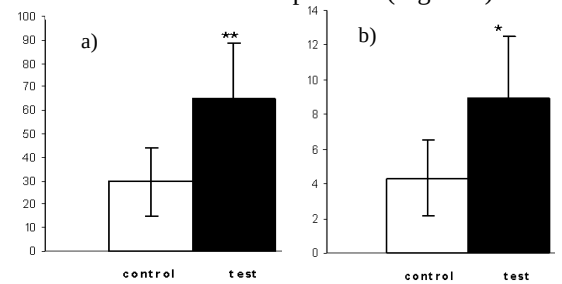

Figure 2: Effect of Vitamin E (0.3ml/day for four weeks) on a) time spent in open arm and b) number of enteries in open arm in plus maze activity. Values are mean±SEM(n=6) significant difference by student t-test ** ($p<0.01$), *($p<0.05$) from water treated controls.

Effects of vitamin E on memory

Morris water maze is used to assess memory. Vitamin E treated rats significantly increase ($p<0.05$) short term memory and also significantly increase ($p<0.01$) long term memory. The time taken by the test animal to reach platform i.e. latency time is significantly less as compare to test animal in short term and long term memory (Figure 3).

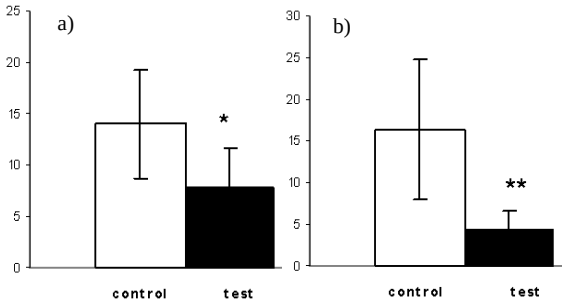

Figure 3: Effect of Vitamin E (0.3ml/day for four weeks) on a) short term memory and b) long term memory in Morris water maze activity.Values are mean±SEM(n=6) significant difference by student t-test *($p<0.05$).**($p<0.05$) from water treated controls

Effect of vitamin E on depression

Swim tank is used to assess depression. Vitamin show antidepressant affect in present study. Vitamin E treated rats significantly ($p<0.05$) decreased floating time and struggling time in swim tank (Figure 4).

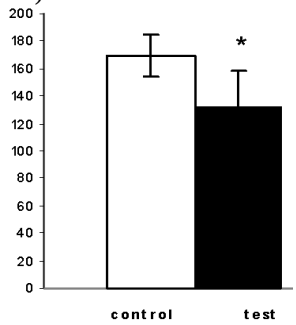

Figure 4: Effect of Vitamin E (0.3ml/day for four weeks) in Swim test activity Values are mean±SEM(n=6) significant difference by student t-test **($p<0.05$) from water treated controls.

Effect of vitamin E on 5HIAA levels

Vitamin E decreases 5HIAA levels. Figure 5 shows that oral administration of Vitamin E significantly ($p<0.01$) decreases 5HIAA levels.

DISCUSSION

In present work, the effects of Vitamin E were studied in several animal behavioural models, such as open-field, plus maze, morris water maze and swim tank. These tests are classical models for screening nervous system actions providing information about psychomotor performance, anxiety and depression[30].

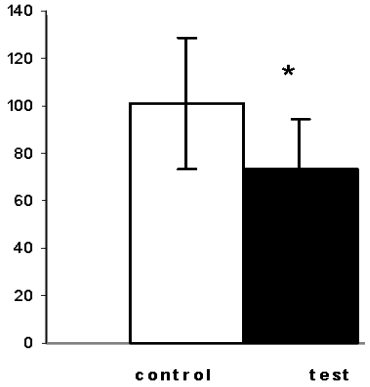

Figure 5: Effect of Vitamin E (0.3ml/day for four weeks) on brain 5HIAA levels.Values are mean±SEM(n=6) significant difference by student t-test * ($p<0.05$) from water treated controls.

Open field behavioural model used to monitor the locomotion and exploratory activity in rats[31] [32]. In present study animals treated with Vitamin E show increased motor activity in open field. The no. of squares crossed in Vitamin E treated animals are greater than their controls. Decrease in latency period was also observed in Vitamin E treated animals , these results show the CNS stimulant activity of Vitamin E.

Anxiety is a fear response for which there is no reason. Disorder may show symptoms, generalized anxiety, panic disorder and obsessive compulsive disorder [33] [34].Chronic anxiety is associated with a higher risk of morbidity and morality from cerebrovascular and cardiovascular diseases, such as hypertension, cardiac ischemia and arrhythmias and it predisposes people to a range of other disorder[35,36]. Therefore the search for new compounds as therapeutic alternatives for such disorders has progressed constantly[37,38]. Elevated plus maze is utilized to assess anxiety[26]. Anxiolytic compounds reduce the animal's aversion to the open arms[30]. In present study Vitamin E treated animal pass greater time in open arm than control which shows the anxiolytic effect of Vitamin E as reported previously that Vitamin E mediate an increase in sedative and antianxiety effect[39]. It is reported that anxiolytic drugs increased[40] or decreased[41] 5HT levels. In present study 5HT levels were not monitored but significantly decrease in 5HIAA levels were observed.

In present study Forced Swim test has been use as an animal model of depression. In present study

Vitamin E treated rats show antidepressant activity. Antidepressent effect of Vitamin E is also reported previously[42,10]. It is observed in the present study that the struggling time is increased in Vitamin E treated animals as compared to their controls. It is previously reported that antioxidant act as antidepressant[43,44]. Antidepressant produce their effect by increasing the availability of 5HT to its receptor[45]. Decreased levels of 5HT[46] and 5HIAA[47] produce depression[48] and increase level of 5HT and 5HIAA produce antidepressent effect[46]. Inhibition of 5HT reuptake by antioxident has been reported[49]. Inhibition of 5HT reuptake increases the 5HT availaibility to its receptor that involve in depression[50]. Decrease 5HIAA levels in depression has been reported[48] Antidepressent activity with decrease 5HIAA levels following Vitamin E administration observed in present study maybe due to inhibition of 5HT reuptake that increases 5HT availability to its receptors as it is reported previously[49].

Learning is a process by which experience change our nervous system and behaviour, these changes are refered to as memory.The present study shows that repeated administration of Vitamin E for four weeks increases short term and long term memory .It has been reported that high intake of Vitamin E improve cognitive function[51] but long term administration produce memory deficits as tested by morrris water maze[52] and improves physical and mental health, increase non specific resistance of body, promote physiological functions and cognition[53,54].

CONCLUSION

In conclusion it is suggested that Vitamin E act as anxiolytic, antidepressive, and also increases memory and exploratory activity. Decreased 5HIAA levels following vitamin E administration produces antidepressant effect.

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