Arch Pharm Res Vol 33, No 3, 463-468, 2010
DOI 10.1007/s12272-010-0317-z

Archives of Pharmacal Research
www.springer.com/12272

The Beneficial Effects of Olibanum on Memory Deficit Induced by Hypothyroidism in Adult Rats Tested in Morris Water Maze

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(Received April 11, 2009/Revised January 7, 2010/Accepted January 13, 2010)

Functional consequences of hypothyroidism include impaired learning and memory and inability to produce long-term potentiation (LTP) in hippocampus. Olibanum has been used for variety of therapeutic purposes. In traditional medicine, oilbanum is used to enhance learning and memory. In the present study the effect of olibanum on memory deficit in hypothyroid rats was investigated. Male wistar rats were divided into four groups and treated for 180 days. Group 1 received tap drinking water while in group 2, 0.03% methimazol was added to drinking water. Group 3 and 4 were treated with 0.03% methimazole as well as 100 and 500 mg/kg olibanum respectively. The animals were tested in Morris water maze. The swimming speed was significantly lower and the distance and time latency were higher in group 2 compared with group 1. In groups 3 and 4 the swimming speed was significantly higher while, the length of the swim path and time latency were significantly lower in comparison with group 2. It is concluded that methimazole-induced hypothyroidism impairs learning and memory in adult rats which could be prevented by using olibanum.

Key words: *Boswellia serrata,* Hypothyroidism, Learning, Memory, Olibanum

INTRODUCTION

There are many reports showing a significant role of thyroid hormones in cell division, maturation, and function of mammalian central nervous system (Timiras and Nzekwe, 1989; Vallortigara et al., 2008). Growth retardation and severe cognitive impairment are produced following thyroid hormones deficiency in the prenatal periods (Porterfield and Hendrich, 1993). Thyroid hormones are also critical for normal adult brain functions (Vallortigara et al., 2008). It has been shown that hypothyroidism is associated with changes of gene expression in both central and peripheral nervous system (Kobayashi et al., 2005). Inability to produce LTP in rat hippocampus and impaired learning and memory in both rats and man are among functional consequences of adult-onset hypothyroidism (Lee et al., 2003). The other researchers believe that hypothyroidism affects behavioral conditions (Burmeister et al., 2001; Smith et al., 2002; Whybrow and Bauer, 2005) and is accompanied by emotional symptoms, including lethargy and dysphoria (Capet et al., 2000; Dugbartey, 1998; Haggerty et al., 1990). The results of other studies show that several cognitive deficits including attention and memory processing deficits, general intelligence and visual-spatial skill are induced by hypothyroidism (Dugbartey, 1998; Osterweil et al., 1992; Smith et al., 2002; Whybrow and Bauer, 2005). Hypothyroidism has less effect on auditory attention, motor skills, language and set-shifting (Burmeister et al., 2001; Dugbartey, 1998; Miller et al., 2007). Even subclinical hypothyroidism is associated with depressive symptoms and cognitive impairment

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(McDermott and Ridgway, 2001).

In ancient traditional medicine, there are many known herbal plants which have been used for their effects on central nervous system. Olibanum is the resin of *Boswellia serrata* authority (family *Burseraceae*) which abundantly grows in dry hilly tracts of India (Sharma et al., 2007) and Eastern Africa (Moussaieff et al., 2005). In ancient texts olibanum has been mentioned as incense or as a major component of incense (Moussaieff et al., 2008). Also it has been used for variety of therapeutic purposes (Gerhardt et al., 2001; Gupta et al., 1998; Gupta et al., 2001; Pandey et al., 2005; Shao et al., 1998; Sharma et al., 1989; Singh and Atal, 1986). To the best of our knowledge, only one study showed that non-phenolic fraction of *Boswellia serrata* has analgesic and psychopharmacological effects (Menon and Kar, 1971). Enhancement of learning and memory following consumption of olibanum is believed in traditional medicine. Taking into account previous findings and pharmacological effects of *Boswellia serrata*, we therefore sought to find any possible effects of *Boswellia* resin (olibanum) on memory deficit of hypothyroid rats by using Morris water maze test.

MATERIALS AND METHODS

Animals and treatments

Twenty eight male Wistar rats (8 weeks old and weighted 200 ± 20 g) were kept at 22 ± 2°C and 12 h light/dark cycle (light on at 7:00 am). They were randomly divided into four groups and treated according to the experimental protocol for 180 days. All measurements were always performed during the first half of the light cycle.

Rats in group 1 (control) received tap drinking water. Group 2 received 0.03% methimazole (Sigma Chemical Co.) in drinking water for 180 days. Groups 3 and 4 were treated with 0.03% methimazole as well as 100 and 500 mg/kg of grinded powder of olibanum in drinking water for 180 days, respectively. Morris water maze test was performed in eight consecutive days at the end of the experiment for all groups.

In order to induce hypothyroidism, the animals received 0.03% of methimazole (Ampong et al., 2002; Leal et al., 2007). Thirty days later, the blood samples of control and methimazole-treated animals were collected from retro orbital sinus and thyroxin level of serum was determined. Thyroxin level was also measured and compared between all groups in the end of experiments.

The olibanum was purchased from India (provided by Zarraya Import & Export Co. Ltd.), identified by pharmacist in Mashhad University of Medical Sciences and then was pounded in a mortar.

The powder (10 g) was mixed with 200 mL of distilled water and stirred at 40°C temperatures and dried to yield 50 mL as a stock solution (Finally, each mL was contained 200 mg of olibanum). For calculation of the first desire volume of water, each rat was located in a separate cage and the mean of volume of drinking water used by each rat was measured for 3 days. Then the concentration of drugs was calculated according to this volume and was used to dilute the appropriate amount of stock solution. For better solubility of olibanum dimethyl sulfoxide (DMSO, final concentration 0.2% v/v) was used. This concentration did not have any effect on learning and memory (Sharifzadeh et al., 2007). For the other days the concentration of drug was prepared according to volume of drinking water used by each rat in previous day. During the experimental period the concentration of methimazole was calculated at the level of 0.03% in drinking water used by the rat.

Morris water maze apparatus and procedures

A circular black and transparent pool (150 cm diameter×60 cm high and 30 cm deep) was filled with water (20~24°C). A circular platform (10 cm diameter× 28 cm high) was placed within the pool, submerged approximately 2 cm below the surface of the water in the center of southwest quadrant. The experimenters, computer and extra-maze cues remained constant throughout testing, lighting in the room was 30~50 lx (Monteiro et al., 2005; Alaei et al., 2007).

Before starting the experiments, each rat was handled daily for 3 days and then the rats were accustomed to the water maze for 30 sec without a platform. The animals performed four trials on each of the eight consecutive days and each trial began with the rat being placed in the pool and released facing the side wall at one of four positions (the boundaries of the four quadrants, labeled N, S, E and W). Release positions were randomly predetermined. On each trial, the rat was allowed to swim until it found and remained on the platform for 15 sec. If 90 sec had passed and the animal had not found the platform, it was guided to the platform by the experimenter and allowed to stay on the platform for 15 sec. Then the rat was removed from the pool, dried and located in its holding bin for a period of 5 min. The speed and time latency to reach the platform and also the length of swimming path were recorded semi-automatically by a video tracking system (Monteiro et al., 2005; Alaei et al., 2007).

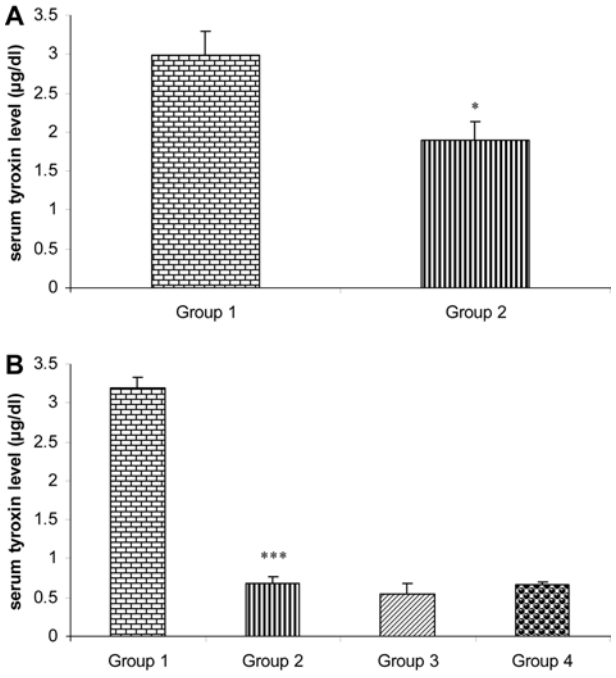

Fig. 1. Serum thyroxin level (µg/dl) in groups 1 and 2 (**A**) in 30th day and serum thyroxin levels in the end of experiment in four groups (**B**). Rats in group 1 received tap drinking water, group 2 0.03% methimazole, group 3 0.03% methimazole plus 100 mg/kg of olibanum and group 4 500 mg/kg of olibanum. Data are shown as mean ± SEM (n=7). *p < 0.05, ***p < 0.001 compared with group 1.

Statistical analysis

The data were expressed as mean ± S.E.M. and were analyzed by repeated measure and Tukeys post hoc test. Comparing the serum thyroxin level was carried out using unpaired t test and ANOVA. The criterion for statistical significance was $p < 0.05$.

RESULTS

After 30 days, the serum level of thyroxin in methimazole-treated animals was compared with group 1 (control). The serum level of thyroxin in methimazole-treated animals was significantly lower than control group (p<0.05) (Fig. 1 A). Fig. 1 B shows the comparison of thyroxin levels between four groups at the end of experiments. As shown, the thyroxin level was significantly decreased in group 2 in comparison with group 1 (p<0.001), but there was no significant difference between groups 3 and 4 compared to group 2. The swimming speed of animals to reach the platform in group 2 after 180 days treatment by methimazole, was significantly lower than group 1 (p<0.001) (Fig. 2). Moreover, the length of swimming path during 8 days and time latency were significantly

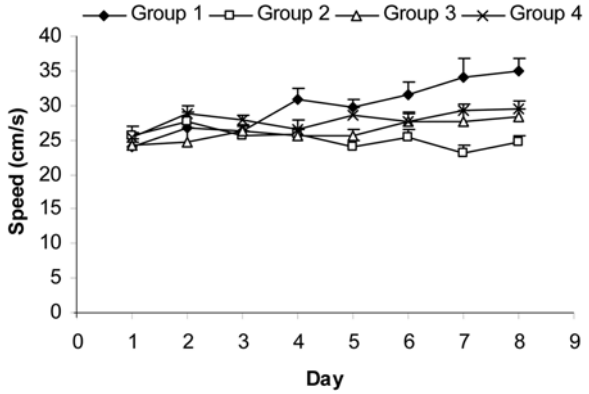

Fig. 2. Comparison of the swimming speed (cm/s) between groups 1~4 using repeated measure ANOVA. The swimming speed in group 2 was significantly lower than group 1 (p < 0.001), while in groups 3 and 4 it was significantly higher than group 2 (p < 0.001). Group 1=control, Group 2=methimazole, Group 3=methimazole+olibanum (100 mg/kg) and Group 4=methimazole+olibanum (500 mg/kg). Data are shown as mean ± S.E.M. of 7 animals in each group.

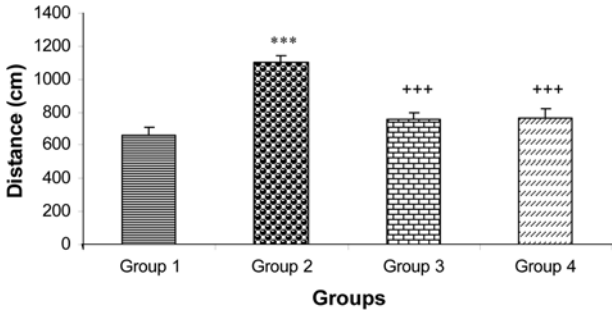

Fig. 3. The length of swimming path (cm) in groups 1~4 during 8 days. ***p < 0.001 compared to group 1, ^{+++}p < 0.001 compared to group 2. Data are shown as mean ± S.E.M. (n= 7).

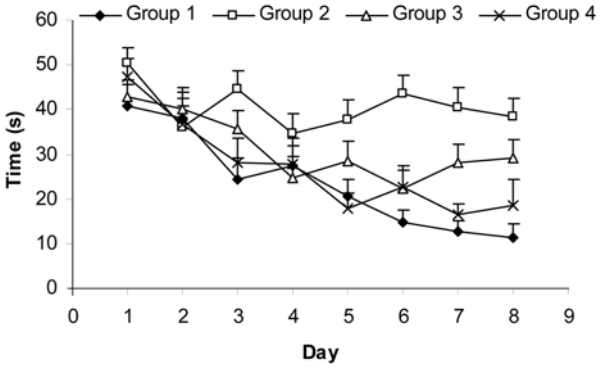

Fig. 4. Comparison of the latency time (sec) between groups 1~4. The latency time was significantly higher in group 2 compared to group 1 (p < 0.001), while in groups 3 and 4 it was significantly lower than group 2 (p < 0.001). Group 1= control, Group 2=methimazole, Group 3=methimazole+olibanum (100 mg/kg) and Group 4=methimazole+olibanum (500 mg/kg). Data are shown as mean ± S.E.M. of 7 animals in each group.

higher in group 2 in comparison with group 1 ($p < 0.001$) (Fig. 3 and 4). The swimming speed of animals in two groups (3 and 4, treated with two doses of olibanum) was compared with methimazole-treated animals (group 2). As shown in Fig. 2, the speed was significantly higher ($p < 0.001$) in groups 3 and 4 compared with group 2. Also the length of swimming path and time latency to reach the platform in groups 3 and 4 were significantly lower ($p < 0.001$) in comparison with group 2.

DISCUSSION

In the present study the effect of olibanum on memory deficit induced by hypothyroidism was investigated. Our results showed that administration of 0.03% methimazole could induce hypothyroidism in adult Wistar rats which is in good agreement with previous findings (Ampong et al., 2002; Leal et al., 2007).

There are some evidences that adult-onset hypothyroidism is clearly linked to cognitive dysfunction (Dugbartey, 1998; Haggerty et al., 1990; Smith et al., 2002; Whybrow and Bauer, 2005). For example, adult-onset hypothyroid rats exhibit spatial memory and learning deficits (Alzoubi et al., 2006; Gerges et al., 2004) and also memory performance, visual-spatial abilities, and aspects of attention are impaired in adult human (Dugbartey, 1998). Hypothyroidism impairs hippocampus-dependent learning, short-term and long-term memory (Gerges et al., 2004), as well as early and late phases of LTP (Alzoubi et al., 2006). However, the exact mechanisms of memory deficit in adult onset hypothyroidism were not clearly revealed. Loss of neurons in dentate gyrus and CA3 hippocampal regions in rats has been reported to be induced by adult-onset hypothyroidism (Desouza et al., 2005; Ambrogini et al., 2005; Alva-Sánchez et al., 2002).

It has been shown that the adult onset hypothyroidism induces oxidative stress in the hippocampus (Cano-Europa et al., 2008). Furthermore the basal levels of phosphorylated ERK1 and ERK2 were decreased in CA1, which could account for hypothyroidism-induced impairment of LTP (Gerges et al., 2004). Decrease of c-jun and c-fos protein levels, changes in expression of other proteins such as synapsin I, synaptotagmin I, syntaxin in hippocampus and finally disturbance in neurotransmitters release may also be involved (Dong et al., 2005; Vara et al., 2002).

It is also suggested that thyroid hormone deficiency results in changes in brain regions such as the dorsal hippocampo-mPFC pathway as well as glutamate release inhibition which finally lead to cognitive disturbances (Shuaib et al., 1994; Sui et al., 2006). In addition, one study showed that vesicular glutamate transporter 2 (VGLUT2) significantly was increased in hypothyroid rats following a three-week treatment with methimazole in the drinking water (Hrabovszky et al., 2004). This may be resulted in glutamate deficiency in glutamate synaptic level and impaired learning. In present study, we have shown that chronic deficiency of thyroid hormones could impair learning of adult rats in Morris water maze test. However, the result of present study may be an only behavioral evidence but Morris water maze is an experimental method which is commonly used to evaluate spatial learning and memory in animal models (Morris, 1984; Nunez, 2008; Schutová et al., 2008).

The results of the present study shows that olibanum prevents learning impairment of hypothyroidism in adult rats. There are only a few studies regarding the effect of *Boswellia* species resin on learning and memory. It has been reported that, while conditioned avoidance response is not affected in trained rats by non-phenolic fraction of *Boswellia serrata*, the secondary conditioned response is blocked (Menon and Kar, 1971). Previous study found that the offsprings whose mothers were administrated aqueous extract of *Boswellia serrata* during gestational period, had better learning and memory performance associated with an increase in the somal volume of hippocampal neurons in CA3 region (Hosseini-sharifabad et al., 2004; Hosseini-sharifabad and Esfandiary, 2005). To date, there is no study to show the effect of olibanum on memory deficit due to hypothyroidism in order to compare with the results of this research. It is impossible that the beneficial effects of olibanum on learning seen in the present study be due to its direct effects of the thyroid hormones because there was any significant difference between methimazole and olibanum treated animals in thyroxin level. The compounds and precise mechanism responsible for the efficacy of *Boswellia serrata* are still remains as an important subject and needs to be clarified by further studies.

CONCLUSION

The results of present study showed that hypothyroidism induced by methimazole significantly reduced learning and memory of adult rats tested in Morris water maze. This deficiency was prevented by using olibanum. Our result supports the traditional belief about beneficial effect of olibanum on learning and memory. Moreover for more clarification of this effect

further investigations using other methods are recommended in future studies.

ACKNOWLEDGEMENTS

Authors would like to thank the Vice Presidency of Research of Mashhad University of Medical Sciences, for financial supports.

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