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Cognitive Improvement by Duloxetine Administration in demented adult APP/PS1 transgenic AD mouse model

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ABSTRACT : *Alzheimer's disease (AD) are often associated with memory and cognitive deficits. Effective treatment of these diseases leads to a marked improvement in the cognitive function of such patients.*
There is a suggestion that there is some neuroprotective properties of duloxetine, as one of the antidepressants, against dementia-associated with cognitive disorders. The present study assessed cognitively enhancing property of duloxetine in a demented adult APP/PS1 transgenic mouse model of AD. Intraperitoneal (ip) administration of a single dose of duloxetine 10 mg/kg/day before each test. This drug treatment rescued cognitive deficits in APP/PS1 mice in both cognitive tests used in this study. The results of the present study suggest that duloxetine administration can help in improvement of cognitive disorder and may inhibit any memory impairement that accompanied the pathogenesis of AD.

I. INTRODUCTION

Cognitive impairment should be considered as an important sign as other emotional and physical symptoms in patients with many mental diseases (Schaffer et, 2000). Duloxetine hydrochloride is a drug that was approved to be an antidepressant medication via inhibition of both serotonin (5-HT) and norepinephrine reuptake (Su et al, 1994). An interesting idea about the possible dual beneficial effect of antidepressant drugs in the treatment of depression with cognitive impairment via the correction of the imbalance or deficiency in 5-HT and/or norepinephrine systems was created as a hypothesis in the last century by many researchers related to improvement of associated cognitive deficits with major depression (Matsuyama et al, 1983) . Duloxetine is an antidepressant drug that researchers try all the time to prove its "dual-action" as both antidepressant and a drug with cognitive and memory improvement "inootropic drug". However, no recent experimental studies have specifically focused on the possible cognitive and memory improvement of duloxetine in the treatment of depressed mood (Raskin et al, 2007 and NIH, 2013).
Because the effect of duloxetine on cognitive performance who commonly suffer from mental disorders has not markedly evaluated, the primary objective of the present study was to assess the cognitive and memory efficacy of duloxetine, that was administered in a dose of 10 mg/ day ip before each test in a demented adult APP/PS1 transgenic mouse model of AD.

II. MATERIAL & METHODS

Animals

Demented adult APP/PS1 transgenic AD mouse model 25-30 gm (3 months old) were purchased from Animal House of Abou-El-Reech animal Institute, Giza, Egypt. They were stored kept in a temperature (22~24oC) and humidity (50~60%) controlled central animal house facility under light (12 h) and dark (12 h) illumination cycle. Animals were given free access to standard food and water. Experiments were performed between 12.00-16.00 h. Each mouse was exposed to elevated plus maze (EPM) and Morris water maze (MWM). In each set, animals were randomly distributed into 2 groups (n=6/group). The arena of EPM was cleaned using 70% ethyl alcohol solution before placing each mouse.

Ethics

Experimental protocols used in present were approved by the Institutional Animal Ethics Committee, Faculty of Medicine, Ain shams university, Cairo, Egypt.

Duloxetine treatment and animal grouping

Duloxetine hydrochloride (Sigma Chemical Co, USA), wase administered through intra-peritoneal route (ip). Normal saline (0.9% w/v NaCl) was used to prepare drug solution. Each mouse received treatment 1 h before test session in EPM (on 2nd day) and Morris water maze (MWM- on 6th day). There were 2 groups of in a demented adult APP/PS1 transgenic mouse model of AD mice:

Control group (Group I), as in a demented adult APP/PS1 transgenic mouse model of AD, received normal saline (10 ml/kg). Treated-group of a demented adult APP/PS1 transgenic mouse model of AD (Group 2) was administered with duloxetine (10 mg/kg).

Spatial memory tests

EPM: The protocol used to evaluate transfer latency (TL) in EPM was described by Dhingra et al, 2004. Time taken by each animal to reach the closed arm is recorded as the TL. In brief, 2 open arms (30×5 cm) and 2 closed arms (30×5×12 cm) of EPM were arranged so that the 2 closed arms kept opposite to each other with an open roof. Each animal was placed at the end of open arm facing away from central platform (5×5 cm). On the first day (the acquisition session), each animal was exposed to EPM for 90 seconds. Time taken by animal to reach the closed arm was recorded as the transfer latency (TL). Animals failed to enter in closed arm in 90 seconds were excluded from study. On second day (the retention session), each animal was put into the open arm and the TL was recorded for maximum 90 seconds. The SMART v2.5.21 video- tracking system (Panlab Harvard Apparatus, spain purchased from Al-Amyria Medical Instrument company, Giza, Egypt) was used to evaluate TL.

Morris water maze (MWM):

MWM test is used to evaluate the hippocampal-dependent learning, including acquisition of spatial memory and long-term spatial memory. The protocol of MWM described by Bromley- Brits et al. (2011) was used to determine the percent time spent in target quadrant. Drug treatments were given to mice 60 min before test on 6th trial day. In brief, the pool having 150 cm diameter and, 50 cm depth was constructed of seamless black polyethylene. The clear plastic escape platform (10 cm diameter, 31 cm high) could be positioned in the any 1 of 4 quadrant position in the pool. The water temperature was maintained at room temperature (22~24oC). Each animal went through training trials (5 trials every day) from day 1 to day 5. On 1st day, platform was visible (1 cm above water level) and placed in south-west, north-west, north- east, centre, and south-west positions in 5 trials, respectively. Starting directions of animal in 5 trials were south (S), north (N), S, east (E), and west (W), respectively. On 2~5th days, platform was made hidden (at water level) and kept in S-W position. The starting locations of each animal in 5 trials were W-S-N-E-S (2nd day), N-E-W-W-S (3rd day), N-E-W-S-N (4th day), and E-S-W-E-N (5th day). On the 6th day, only 1 trial was performed having N as starting location of animal and without platform. The time spent in target quadrant (SW) was noted as index of retrieval or memory. Video camera was fixed on the ceiling to record the behavior of the mice in the pool. It was interfaced with the SMART v2.5.21 video-tracking system (Panlab Harvard Apparatus, spain also purchased from Al-Amyria Medical Instrument company, Giza, Egypt).

Statistical analysis

The Graphpad Prism Windows version 5 was used to perform statistical analysis. Comparison between different groups was performed using ANOVA followed by Tukey's test to determine the significant difference as a post-hoc test. Data was represented as mean±SD values (per group n=6/group). The level of significance was $p<0.05$.

Results

1. Figure (1). Showed the period of Elevated plus maze - Transfer Latency (TL) in both tested groups.

   There was a marked reduction in TL in duloxetine-treated group as mean± SD (80±6.5 sec. in control group versus 34.17±4.8 sec. in duloxetine-treated group). There is a percentage reduction by 57.29 sec in TL by duloxetine treatment in such transgenic model.

   2- Figure (2):

   Morris water maze. (A) Escape latency (visible platform) measured on 1st day. (B) Escape latency (invisible platform) measured between 2nd and 5th days. (C) Time spent in target quadrant on 6th day. Data is presented as mean±SD (n=6/group).

   There was a marked reduction in any delay induced* in the control group compared to duloxetine-treated group as mean± SD (51.61±2.7 sec. in control group versus 19.94±2.0 sec. in duloxetine-treated group). There is a percentage reduction by 61.36 sec in any delay in movement by duloxetine treatment in such transgenic model.

III. DISCUSSION

The results of the present study suggest that duloxetine administration can help in improvement of cognitive disorder and may inhibit any memory impairement that accompanied the pathogenesis of AD, after its administration in a dose of 10 mg/kg ip in a demented adult APP/PS1 transgenic mouse model of AD . Fuller et al, 1994 revealed that duloxetine, (+)-N-methyl-3-(1-naphthalenyloxy)-2-thiophenepropanamine, is an inhibitor of the serotonin and norepinephrine neuronal transporters. In their tested mice, duloxetine antagonized the depletion of brain serotonin by p-chloroamphetamine (ED50 = 2.5 mg/kg, i.p.) and the depletion of heart norepinephrine by 6-hydroxydopamine (ED50 = 1.1 mg/kg, i.p.). Brain concentrations of 5-hydroxyindoleacetic acid were decreased by duloxetine at 2 hr after doses of 1, 3 and 10 mg/kg and at 1 to 8 hr (but not 24 hr) after a 10 mg/kg i.p. dose of duloxetine. Duloxetine antagonized norepinephrine depletion in frontal cortex, but not dopamine depletion in striatum, after treatment of mice with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. In rats, duloxetine decreased brain 5-hydroxyindoleacetic acid dose-dependently for up to 8 hr and decreased serotonin turnover measured by the accumulation of 5-hydroxytryptophan in rat hypothalamus after decarboxylase inhibition. In rats, duloxetine antagonized the depletion of brain serotonin by p-chloramphetamine and the depletion of norepinephrine and epinephrine in hypothalamus after the injection of 6-hydroxydopamine. In vitro, duloxetine had little effect on either type A (serotonin as substrate) or type B (phenylethylamine as substrate) monoamine oxidase, IC50 concentrations being above 10(-5) M. These data extend evidence that duloxetine inhibits serotonin and norepinephrine transporters in vivo, actions that may lead to therapeutic efficacy in mental depression.

The reduction in escape latency observed from the first day to 5th day as shown in figure 2, is supported by clinical studies that have reported cognition related benefits with 8 weeks (Raskin et al, 2007) and 12 weeks (Greer et al, 2014) of duloxetine treatment in depressed patients. Many published reports showed that there is a significant increase in brain monoamine profile of duloxetine including norepinephrine, serotonin and other chemical neurotransmitters (Kihara& Ikeda, 1995 and Muneoka et al, 2009). These reports suggest also that duloxetine increases dopamine (DA) levels not only in cerebral cortex (Kihara& Ikeda, 1995 and Muneoka et al, 2009) but also in hippocampus (Kale & Addepalli, 2014) and nucleus accumbens region (Muneoka et al, 2009). Frontal cortex and hippocampus regions play important role in cognition and emotions (Eriksson et al, 2012). The possible reason behind the ability of duloxetine to produce augmentation of nootropic activity that appears in the marked cognitive and memory functions in this model of transgenic mice may be the interactions between the increase in serotonin and norepinephrine and duloxetine in the important brain's area for both functions, the hippocampus (Greer et al, 2014). Older generation of antidepressants as tricyclic antidepressants, amitriptyline showed a reduction in memory and learning tasks due to a low action of amitriptyline serotonin and norepinephrine re-uptake as suggested by Everss et al, 2005 .

IV. CONCLUSION

Further studies that would focus on the effect of acute and chronic dosing of duloxetine on electrophysiological analysis, neurogenesis, biogenic amine pathway activation/deactivation, drug metabolism, and related drug interaction studies may help in supporting the results of the present study outcomes that would benefit the patients with AD.

Disclosure

The author reports no conflicts of interest in this work.

V. ACKNOWLEDGMENT

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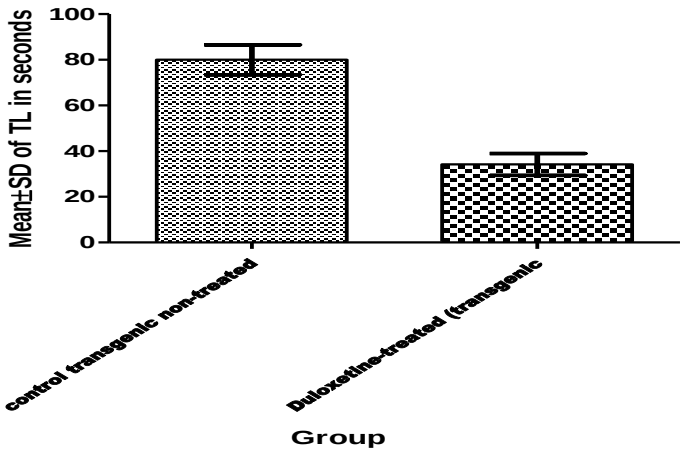
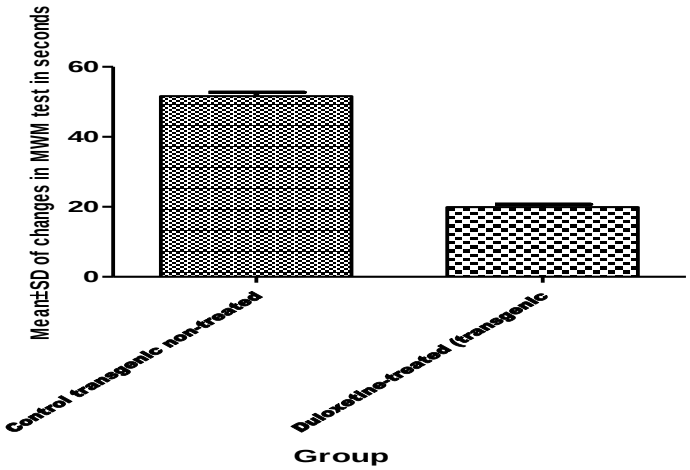
Figure (1)



*p<0.05 as a significant difference - as compared to the control group (n=6/group).

Figure (2)



*p<0.05 represents significant difference - as compared against the control group.