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Abstract: Major depressive disorder (MDD) is the leading cause of memory impairment in general population. The serotonin hypothesis provides a target model for the treatment of depression and depression-associated memory loss. 5-HT-1B receptor is suggested as a potential candidate in the pathophysiology of depressive illness. Dysfunction of 5-HT-1B receptors has been observed previously in depressive patients. Zolmitriptan, 5-HT-1B agonist is clinically recommended for the treatment of migraine. However, in present study this drug was tested as a potential treatment for depression and associated memory loss by altering the serotonergic function at receptor level. Rats (n=24) were equally divided into unstressed and stressed groups. Depression was induced by 19 days of restraint stress for 4 h which was followed by forced swim test and pattern separation test to assess depressive symptoms and memory impairment, respectively. The initial sign of depression-associated memory loss involves impaired pattern separation which is regarded as pseudodementia. In this study stressed rats showed depression- and pseudodementia-like symptoms. After the induction of depression, rats were treated with zolmitriptan at a dose of 0.3 mg/kg which resulted in a significant attenuation of depression and depression-associated memory impairment. Results are discussed with reference to the modulation of function of 5-HT-1B receptor following the administration of exogenous agonist.

Keywords: 5-HT-1B receptors, depression, pseudodementia, zolmitriptan.

INTRODUCTION

Major depressive disorder (MDD) is the life threatening disease. The estimated risk factor for the occurrence of MDD in female is about 20-25% and in males it is about 7-12% (Svenningsson *et al*., 2013). The complete pathophysiology of depression is still not identified, however, serotonergic abnormalities have been frequently implicated (Svenningsson *et al*., 2006). In depressive patient abnormal functioning of 5-HT receptors, including 5-HT-1B, has been reported previously. The 5-HT-1B receptors are involved in various physiological responses including satiety, temperature regulation and memory formation (Tiger *et al*., 2018). Beside these, the possible role of 5-HT-1B in psychiatric illnesses has also been suggested. Reduced expression of 5-HT-1B receptors has been reported previously in animal model of depression, moreover, diminished p11 intracellular signaling associated with 5-HT-IB has been observed in postmortem brains of depressed persons (Murrough *et al*., 2011). The p11 intracellular protein is involved in physiological function of 5-HT-1B receptors (Eriksson *et al*., 2013). Anxiolytic effects are the characteristic outcome of 5-HT-1B receptors, however, antidepressant effects of 5-H-1B agonist are also reported (Tatarczyńska *et al*., 2004). Preclinical study on rodent model of depressive symptoms showed the increased efficacy of antidepressant drugs when administered along with the treatment of 5-HT-1B agonists (Ruf and Bhagwagar *et al*., 2009). Clinical studies conducted on MDD patients also showed the contribution of 5-HT-1B receptors in depression and responsiveness of these receptors when the patients were treated with antidepressant drugs (Tiger *et al*., 2018). Zolmitriptan is 5-HT-1B agonist which is recommended for the treatment of migraines. The anti-migraine effects of zolmitriptan are due to vasoconstriction. It inhibits increased cerebral blood flow triggered by trigeminal nerves. After crossing the blood brain barrier, it obstructs trigeminovascular activation in the brainstem (Martin *et al*., 1997). The 5-HT-1B receptors are mainly present on presynaptic sites, however, they also regulate the release of other neurotransmitters and function as heteroreceptors. Antidepressant-like effects of activation of 5-HT-1B heteroreceptors in a rodent serotonin-depletion model has been observed previously (Nautiyal and Hen *et al*., 2017). 5-HT heteroreceptors give response to the relevant 5-HT receptor ligand which may result in increased release of specific neurotransmitter. This can explain its hypothesized deficit in distinct brain areas (Fink and

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Göthert *et al*., 2007). The implication of these receptors in memory formation has also been reported. Improved memory function has been reported in mice following the stimulation of 5-HT-1B receptors by the administration of agonist (Eriksson *et al*., 2013). Depression and memory disturbances are co-associated. The memory loss secondary to depressive illness is particularly called as pseudodementia (Kang *et al*., 2014). Pseudodementia is considered as the precursor of true dementia and if it remains untreated then there are chances that it may lead severe memory loss in later stages. It has been suggested that if the underlying psychiatric illness is treated then pseudodementia can be reversed (Kennedy, 2015). 5-HT-1B receptors are implicated in psychiatric illness and antidepressant effects of 5-HT-1B agonists are also reported previously. Hence, the current experiment was designed to study the function of 5-HT-1B receptors in depression. Furthermore, the study also aimed to determine the role of 5-HT-1B receptors in memory impairment associated with depression in rats.

MATERIALS AND METHODS

Animals

Twenty four locally bred male albino Wister rats weighing 150-180 grams purchased from Animal Facility of International Center for Chemical and Biological Sciences, University of Karachi, weighing about 180-200 g. Animals were kept individually in their cages in a quiet room for at least a week so that the rats adapt to the laboratory environment. Experiment was approved by institutional Board of Advance Studies and Research (BASR no: 03344/Sc), University of Karachi and performed in accordance with National Institute of Health Guide for Care and Use of Laboratory Animals (Publication No. 85-23, revised 1996). All experimental procedures were made in a balance design to avoid the effect of time and order.

Drug

Zolmitriptan was used in the experiment purchased from Sigma Aldrich. Drug was prepared in distilled water and administered to the test animals at the dose of 0.3 mg/kg orally. Untreated rats received an equal volume of distilled water. Effects of zolmitriptan were monitored after 30 min of treatment as it has been reported to produce effects within half an hour when administered orally (Bahra *et al*., 2000).

Experimental protocol

Animals ($n = 24$) were randomly divided into two experimental groups control ($n = 12$) and test ($n=12$). Test was subjected to chronic restraint stress in restrainer tube following the procedure as reported earlier (Nawaz *et al*., 2017). The stress procedure was continued for 19 days for 4 h daily till the appearance of depressive symptoms in rats. Depression was assessed by forced swim test (FST). After developing depression-like symptoms in rats, pattern separation test for similar new object (PST-SNO) and pattern separation for different location of object (PST-DLO) were monitored. Morris water maze (MWM) test was also conducted to monitor spatial memory. After collecting the behavioral data, both groups were further divided into two groups. One was treated with saline whereas second was administered with zolmitriptan orally at the selected dose. After 30 min of administration rats were again subjected to behavioral analyses including FST, PST-SNO, PST-DLO and MWM. Behaviors were performed between 0900-1500 h. All procedures were conducted in a balanced design to minimize the effect of order and time. Results of behavioral testing before and after the drug treatment were reported at the end of the experiment.

Behavioral protocols

Assessment of depression-like illness

Expression for depression was monitored by FST paradigm. The apparatus and procedure was essentially same as described previously (Nawaz *et al*., 2017).

Pattern separation for similar new object (PST-SNO)

This test was conducted to evaluate the ability of rats to differentiate between similar but new objects. This test has been suggested to determine the tendency of pattern separation to identify the minute differences between two different objects. The apparatus consisted of an open field 40×40×40 cm. The test comprised of three sessions; habituation, familiarization and test sessions. During habituation, each rat was placed in the box and allowed to explore the area for 10 min in order to habituate with the box. After 24 h of habituation, two similar objects were placed in the box and rat was allowed to explore both objects for 5 min so that rat got familiarized with both objects. Test session was carried out after 20 min of familiarization phase during which one of the object was replaced by a new but similar object. The old object which was not replaced was designated as ‘a’ whereas the new object was assigned as ‘b’. During test session exploring time for each object was recorded. Discrimination index (DI) was calculated by using the formula (b-a/a+b), where ‘a’ is the time to sniff the old object and ‘b’ is the time to sniff the new object placed during test session. This test based on the recognizing ability of rodent using olfactory cues. The discrimination index ranges between -1 to +1. The lower values of DI represent inability of rat to differentiate between similar but new objects.

Pattern separation test for different location of object (PST-DLO)

This test was also used to analyze the ability of pattern separation in rats. This test was based on the ability to discriminate similar events from one another (van Hagen *et al*., 2015). In this test an apparatus having the

dimension of 76×76×42 was used as an open field area. This test also comprised of three sessions; habituation, familiarization and test sessions. Rat was allowed to habituate with the open field arena during habituation for 10 min which was followed by familiarization phase after 24 h. During familiarization two massive and identical (12×12×12 cm) wooden blocks were placed in the middle area on a same horizontal line. Rat introduced into open field area facing towards the wall and was allowed to explore both objects for 5 min. After 20 min of second phase, test session was conducted during which one of the objects was displaced from its position to a definite point in order to change its location so that the objects aligned diagonally. Time to sniff both objects was recorded during testing phase. The object which was not displaced from its location was designated as 'a' whereas the object with new location was named as 'b'. DI was calculated by the same formula as mentioned above. DI value ranges between -1 to +1. The impaired pattern separation was determined by lower DI values indicating that rat was unable to identify the new location of displaced object.

Assessment of spatial memory by Morris water maze (MWM)

The dimensions of the apparatus used for MWM and its procedure were same as described earlier (Liaquat *et al*., 2018).

STATISTICAL ANALYSIS

One-way ANOVA followed by Tukey's test for *post hoc* analysis was used for the analysis of data before and after the treatment of zolmitriptan. FST, PST-SNO, PST-DLO, MWM were included in this analysis. Values of $p<0.05$ were considered as a statistically significant difference.

RESULTS

Effects of stress and zolmitriptan on FST

In present study depression-like behavior was monitored by using FST paradigm before and after treatment of zolmitriptan. Test was conducted after 19 days of stress exposure. It was observed that there were significant effects of stress on struggling time [$F_{(3, 20)}$ =20.033] and immobility time [$F_{(3, 20)}$ =7.736]. Nineteen days of stress exposure significantly induced depression-like symptoms in rats. DEP group showed decreased struggling time and increased immobility time as compared controls. Zolmitriptan treatment was started after observing the depressive symptoms. Depression was again analyzed after single dose of zolmitriptan and data showed significant effects of zolmitriptan treatment on struggling time [$F_{(3, 20)}$ =16.963] and immobility time [$F_{(3, 20)}$ =7.593]. Depression (DEP) group showed significantly decreased struggling time and increased immobility time as compared to control group whereas zolmitriptan treatment significantly reduced depression-like symptoms in depression + zolmitriptan (DEP+Zolmi) group. This group performed well in FST paradigm and showed significantly increased struggling time and decreased immobility time when compared to DEP group.

Effects of stress and zolmitriptan on PST-SNO

Effect of depression on pattern separation was observed by PST-SNO. In this test discrimination between similar new objects was analyzed. It was observed that depression causes significant impairment in pattern separation [$F_{(3, 20)}$ = 78.98]. DEP group showed decreased values of DI as compared to controls. After zolmitriptan treatment there was significant increase in DI [$F_{(3, 20)}$ =51.142]. DEP group were unable to discriminate between similar new object as compared to control group. Whereas, DEP + Zolmi group significantly distinguished between similar new object as compared to DEP group.

Effects of stress and zolmitriptan on PST-DLO

There was another parameter of pattern separation named as PST-DLO in which discrimination between different locations of object was monitored. It was observed that DEP group were unable to distinguish the change in location of object [$F_{(3, 20)}$ =17.506]. DEP groups showed decreased values of DI as compared to controls. After zolmitriptan treatment there was significant increase in DI [$F_{(3, 20)}$ =18.369]. Zolmitriptan treatment ameliorated pattern separation impairment as DEP + Zolmi group showed improved pattern separation as compare to DEP group.

Effects of stress and zolmitriptan on MWM

MWM test was used for the evaluation of spatial memory. It was observed that depression menace the spatial memory. MWM showed significant decrease in time spent in target quadrant [$F_{(3, 20)}$ =14.525]. DEP group showed significantly decreased time spent in target quadrant as compare to control group. There was no significant difference in latency to reach target quadrant. After zolmitriptan treatment time spent [$F_{(3, 20)}$ =8.038] and latency to reach target quadrant in target quadrant were [$F_{(3, 20)}$ =40.420]. DEP group spent less time in target quadrant as compared to control and took more time to reach target quadrant as compared to control. Zolmitriptan treated rats performed well in MWM as compared to control rats, time spent in target quadrant was non-significant but they reached more quickly in target quadrant as compared to controls. DEP+Zolmi group spent non-significantly more time as compare to DEP group and reached to target quadrant more quickly as compared to DEP group.

DISCUSSION

Chronic stress is considered as one of the major causes for the onset of depression (Duman, 2014). In present study animals that were exposed to 19 days of chronic restraint

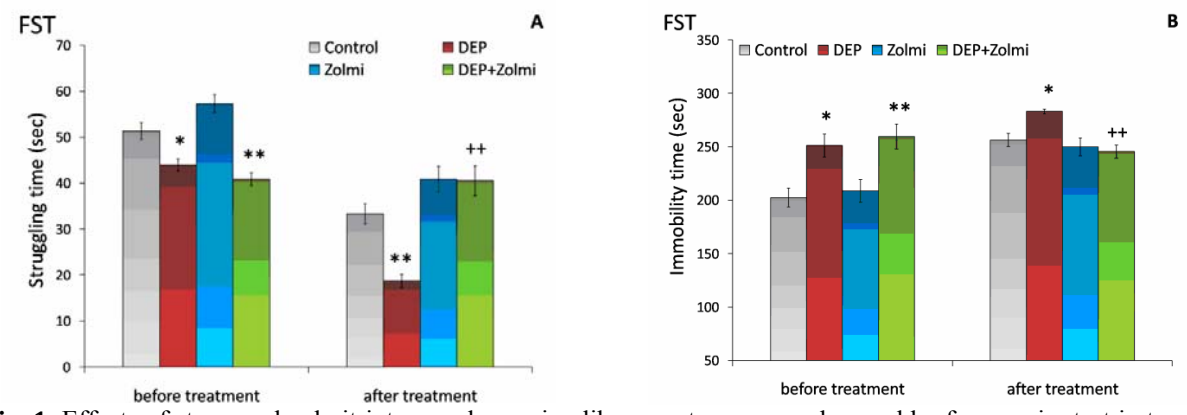

Fig. 1: Effects of stress and zolmitriptan on depressive-like symptoms were observed by force swim test in terms of (A) struggling time and (B) immobility time. Data is represented as mean±SEM (*n*=6). Significant difference were obtained by Tukey's post hoc test; **p*<0.05, ***p*<0.01 as compared to control group; ++*p*<0.01 as compared to DEP + Zolmi group.

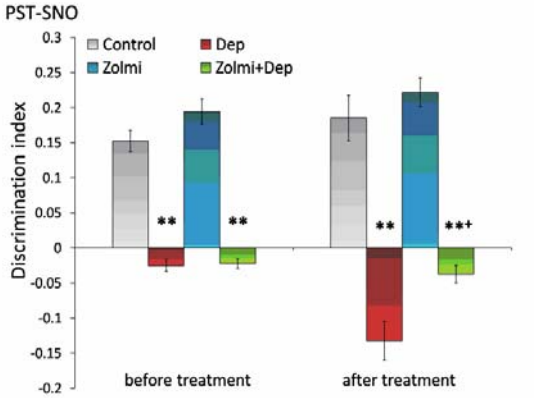

Fig. 2: Effects of stress and zolmitriptan on pattern separation function assessed for similar new object. Data is represented as mean±SEM (*n*=6). Significant difference were obtained by Tukey's post hoc test; ***p*<0.01 as compared to control group; +*p*<0.01 as compared to DEP + Zolmi group.

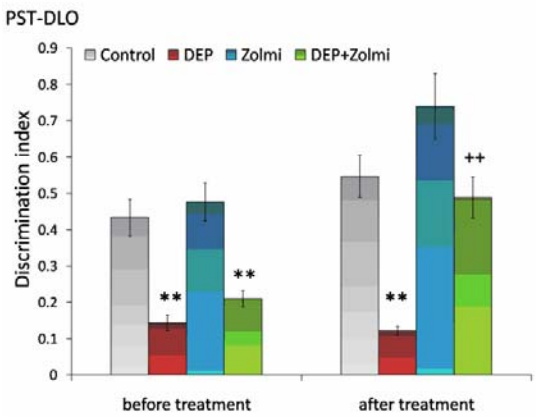

Fig. 3: Effects of stress and zolmitriptan on pattern separation function analyzed for different location of object. Data is represented as mean±SEM (*n*=6). Significant difference were obtained by Tukey's post hoc test; ***p*<0.01 as compared to control group; ++*p*<0.01 as compared to DEP + Zolmi group.

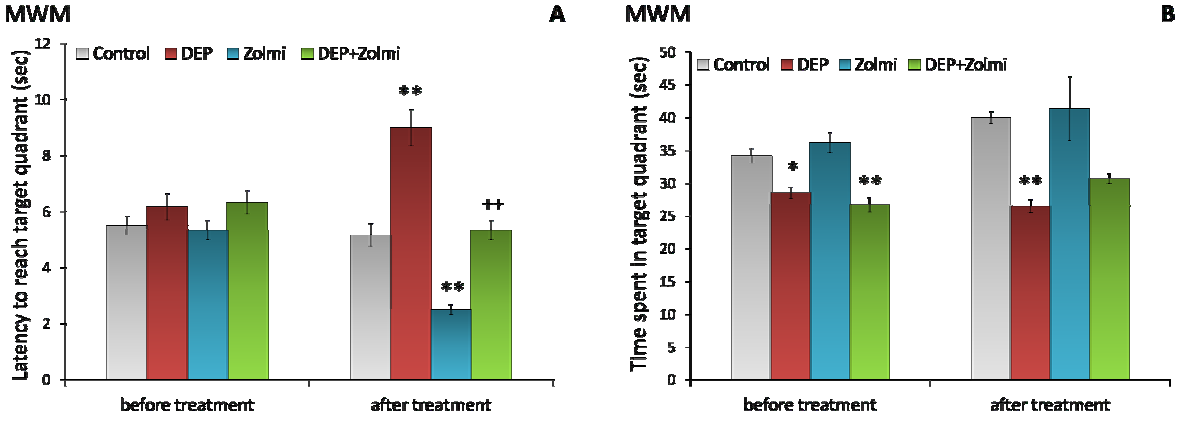

Fig. 4: Effects of stress and zolmitriptan on spatial memory function observed by Morris water maze in terms of (A) latency to reach and (B) time spent in target quadrant. Data is represented as mean±SEM (*n*=6). Significant difference were obtained by Tukey's post hoc test; **p*<0.05 ***p*<0.01 as compared to control group; ++*p*<0.01 as compared to DEP + Zolmi group.

stress showed depression-like symptoms evident by decreased struggling time and increased immobility time observed in FST. Previous studies have reported the implication of 5-HT-1B receptor in the pathophysiology of depression (Ruf and Bhagwagar, 2009). 5-HT-1B agonist CP-94,253 showed biphasic effect on 5-HT release. At low doses it induced decrease in 5-HT release whereas, administration at high doses resulted in increased 5-HT release due desensitization of presynaptic receptors (Adell *et al*., 2001). It has been suggested that down regulation of 5-HT-1B autoreceptor mediates antidepressant effects. In this regard agonist of 5-HT-1B provides a more selective approach for quicker desensitization of 5-HT-IB autoreceptors (Tiger *et al*., 2018). In this study administration of zolmitriptan after the appearance of depressive symptoms in rats significantly reduced behavioral despair in FST paradigm. This suggests the desensitization of 5-HT-1B autoreceptor at the given dose which might have increased the release of 5-HT in synapse and produced antidepressant effects.

It has been shown that depression causes reduction in density of presynaptic and post synaptic memory related proteins in hippocampus, which impairs memory and behavioral responses (Jianhua *et al*., 2016). Studies have reported a number of consequences of depression but in this study depression-associated memory loss was focused. Pseudodementia is a cognitive impairment that includes mood disturbances and reduced performance. It has been suggested that condition can be reversed unlike other psychiatric illness (Tanner at al., 2015). It has been observed that depressive pseudodementia patients can perform better as compared to patients with Alzheimer's and true dementia so, there must be a criteria to find the difference between true dementia and pseudodementia so that it can be treated more accurately (Kang *et al*., 2014). It has been reported that the memory loss due to depression primarily affects the pattern separation and the patient is unable to recognize the difference between two similar but different objects (Gandy *et al*., 2017). In rodents, assessment of pattern separation is specifically designed to monitor pseudodementia (van Hagen *et al*., 2015). In present research it was observed that depressive rats were not capable to distinguish among similar new objects and change in position of objects. The impaired pattern separation ability indicates that some changes occurred in brain which may be related to primary storage capacity of brain or it may be due to poor concentration. It has been described earlier that in depression hippocampal neurotransmission decreased leading to impaired memory function (Eriksson *et al*., 2013). In present study a condition similar to pseudodementia was observed in rats which may be due to the consequence of depression so, it can be postulated that depression causes structural and functional changes in brain that affect memory function and cognition.

It is observed that depression-like illness is related to the reduction in brain 5-HT levels (Lin *et al*., 2014). Previously, it has been shown that activation of 5-HT-1B heteroreceptors produced antidepressant effects in animals (Nautiyal and Hen 2017). One of the 5-HT-1B agonist vortioxetine has shown to be involved in the maturation of neurons and enhanced neurogenesis. It also produced antidepressant effects by repeated administration (Guilloux *et al*., 2013). Activation of the 5-HT-1B receptor in the frontal cortex results in an increase in acetylcholine (Consolo *et al*., 1996). This may explain the reason of zolmitriptan-mediated attenuation of depression-induced memory loss. The current study showed that administration of zolmitriptan 5-HT-1B agonist produced antidepressant effects observed in FST and reversed the condition of pseudodementia. It is well established that increased 5-HT levels reduce depression-like symptoms and hence have positive effects on learning and memory function (Haider *et al*., 2006). In previous research it has been shown that 5-HT-1B receptors are widely present in hippocampal circuitries and they regulate hippocampal neurotransmission. 5-HT-1B receptor ligands therefore can be used for the treatment of cognitive impairment in psychiatric disorders and related cognitive impairment (Eriksson *et al*., 2013). However, further research is needed to justify the role of 5-HT-1B agonists in depression and depression-associated memory loss at different doses as previous data related to the role of 5-HT-1B receptors is contradictory (Yohn *et al*., 2017).

CONCLUSION

It is concluded from this study that 5-HT-1B agonists can be considered for the treatment of depression. In future, however, studies are required to validate the result of this study. The drug, zolmitriptan, used in this study can be used for treatment of depression and to cure depression-associated secondary health issues such as pseudodementia.

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