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Comparison of behavioral effects of selective serotonin reuptake inhibitors, fluoxetine and an herbal antidepressant, St. John's Wort on depression

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Abstract: Investigation on the mechanism of action of traditional antidepressant suggested that they enhance neurotransmission across monoamine (MA) synapse by inhibiting neuronal uptake or degradation of MA. Development and introduction of Specific Serotonin Reuptake Inhibitors (SSRIs) was prompted by the desire to eliminate some side effects of traditional antidepressant. These drugs act by selectively inhibiting the neuronal reuptake of serotonin (5-Hydroxytryptamine, 5-HT). The present work has been planned to compare the antidepressant effect of herbal antidepressant St. John's Wort and SSRI Fluoxetine. As depression is also associated with amnesia, in the present study we also assessed the memory of rats using Water Maze (WM). Both antidepressants were given orally to rats for two weeks. Repeated treatment by both antidepressants significantly reduced the immobility time of rats in Forced Swimming test (FST) and both drugs were equally effective in inducing antidepressant like effects. Memory functions of rats were more enhanced following St. John's Wort as compared to Fluoxetine. In conclusion, the present study suggests that use of St. John's Wort may be more effective in the treatment of depressive conditions as compared to fluoxetine.

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INTRODUCTION

Depressive illness is a disease of middle and old age. Depression refers to a spectrum of mental health problems characterized by persistent sadness or low mood[1], which may be because of the hypoactivity of catecholaminergic or serotonergic system of the brain[2-6]. Depressive disorders are expected to show a rising trend over the next twenty years, and are expected to become an important cause of disability and disease burden by 2020[7] and ranks fourth among causes of death or injury[8]. A role of monoamine neurotransmitter especially serotonin (5-Hydroxytryptamine; 5-HT) in the regulation of mood is well established[9-10]. It has been suggested that changes in brain monoamines (MA) may result in the alteration of mood. A number of studies have shown that depleting MA in the brain could precipitate depression[11-12] while elevating them might have antidepressant effect[3,13].

The mood of an individual with major depression is often described as sad, hopeless, or discouraged, and there are many physical symptoms associated with depression[1]. The therapeutic effect of antidepressants aim at the restoration of mood and behaviors as these antidepressant increases the MA functions[5,14]. MA are also known to be involved in the enhancement of memory functions[15,16] so therefore antidepressants are also effective in improving memory functions[17,18]. The prescription of the new antidepressants such as, selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors and noradrenergic and specific serotonergic antidepressants is increasing compared to that of tricyclic antidepressants. These antidepressants have become a first-line treatment option for millions of patients due to their good balance between efficacy and tolerability. Among various classes of antidepressants, SSRIs are the most beneficial one as they are less likely to cause side effects that are produced by traditional antidepressants[19]. Apart from the synthetic antidepressants herbal remedies have also proved to be effective in the treatment of depression. During the last decades the use of herbal medicines has been tested to alleviate the symptoms of depressive disorders using animal search[20]. One of the herbal medicines for the treatment of depression is St. John's Wort[21]. St John's wort (*Hypericum perforatum*) is one of the most commonly used herbal antidepressants for treatment of mild to moderate depression[22,23]. The name St. John's Wort has its origin in Christian folk tradition. It has a long history of use in traditional European herbal medicine. It was first noted as a remedy for melancholy and madness by Culpeper in 1952. It was officially recognized as an antidepressant drug in Germany in 1998. The present study is designed to compare the behavioral effects of Fluoxetine and St. John's Wort on depression and memory functions in rats.

MATERIALS AND METHODS

Animals

Total 18 adult male albino Wistar rats purchased from Aga Khan University Hospital, weighing

approximately 180g, were housed in individual cages for 7 days for acclimatization to the study surroundings, and allowed free access to fresh water and chow in a temperature-controlled environment of 24°C with a 12-h light, 12-h dark cycle before initiation of the experiment.

Drug administration

The experimental protocol was designed to administer the drugs for 2 weeks. Animals were randomly divided into control and two test groups. One test group received Fluoxetine while other test group received St. John's Wort daily for 2 weeks. Control rats were given an equal amount of water for 2 weeks. Weighed amount of food was placed in the hopper of all the cages. Body weight and food intake were monitored weekly. Behavioral activities of rats were monitored after 2 weeks of drug administration. The experiment was performed in a balanced design in such a way that control and drug treated rats were killed alternately to avoid the order effect.

Behavioral tests

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 in our laboratory[24]. The method is not same as that described by them. It is a modification of their method[25]. 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 (60cmx30cm) filled with room temperature-water opacified with powder milk, to the depth of 12cm. A wooden platform (15cmx13cm) was hidden 2cm below the surface of water in a fixed location. The experiment was performed after 2 weeks of drug administration. 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 1h after training). The cut off time for each session was 2 minutes.

Forced swimming testing and measurement of immobility

This test is most widely used and is recognized pharmacological model for analyzing depression like behavior in rats and mice. The development of immobility when the rats are placed in an inescapable chamber filled with water reflects the cessation of persistent escape directed behavior. During the test session the swimming behavior defined as movement throughout the swim chamber was monitored. The rats were individually forced to swim for 6 minutes in a glass tank (height 56 cm, width 20cm) which contained water to a height of 22cm at 25ºC. The water height was chosen to prevent the animal from touching the bottom of the tank while at the same time preventing escape from the apparatus. The immobility time was calculated as: 360(s)-swimming time(s)=immobility time. Immobility is considered when the rat makes no further attempts to escape and makes only the movements to keep its head above water.

Statistical analysis

Results are presented as mean±SD. Behavioral data were analyzed by one way ANOVA; p- value<0.05 were considered significant.

RESULTS

Effect of fluoxetine and St. John's wort on memory functions in rats

Effect of fluoxetine and St. John's wort on memory functions was assessed one hour after the first trial (Figure 1). Analysis by one way ANOVA showed a significant treatment effect ($F=8.24$, df: 2,15 $p<0.01$). Post hoc analysis showed that memory functions was significantly improved following St. John's wort and fluoxetine. Memory of rats was more enhanced following administration of St. John's Wort as compared to Fluoxetine.

Effect of fluoxetine and St. John's Wort on immobility time of rats

Effect of fluoxetine and St. John's wort on immobility time of rats was monitored by forced swimming test (Figure 2). Analysis by one way ANOVA showed a significant treatment effect ($F=6.13$, df: 2,15 $p<0.05$). Post hoc analysis showed that fluoxetine and St. John's wort both significantly reduced the immobility time of rats.

DISCUSSION

Administration of SSRI fluoxetine and an herbal medicine for depression St. John's Wort for 2 weeks reduced the immobility time of rats in FST, which is especially relevant for assessing the potential antidepressant effect of drug. In the present study St. John's Wort and fluoxetine were equally effective to delay helplessness induced immobility of rats. This could be due to the overall increase of serotonergic neurotransmission caused by desensitization of 5-HT_{1A} autoreceptors[26]. Microdialysis studies in chronically SSRIs treated rats have demonstrated

elevated levels in terminal areas and attenuated ability of 5-HT_{1A} receptors in the raphe nuclei to regulate terminal 5-HT release[27]. One of the cardinal signs of depression is memory impairment[28,29]. The present study also assessed alterations in memory functions of rats by these drugs. Memory of rats have been assesses by using WM. Memory functions of rats administered with St. John's wort was more enhanced as compared to Fluoxetine as evidenced by the decreased latency time to reach the hidden platform in WM.

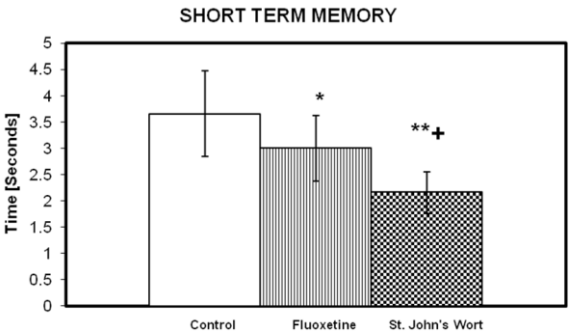

Figure 1: The effect of fluoxetine and St. John's Wort on short term memory functions of rats in water maze test. Values are means ± S.D. (n=6). Significant difference by Newman-Keuls test: *p<0.05 vs control group; **p<0.01 vs control group; +p<0.05 vs fluoxetine treated group following one way ANOVA.

Herbal medicine has grown faster than any other alternative treatment method in United States[30,31]. St. John's Wort is used almost exclusively as herbal antidepressants[21,32]. The mechanism of this drug is unclear[33,34]. It has been suggested that it inhibits monoamine oxidase (MAO). Its mechanism of action is now thought to lie in selective inhibition of 5-HT, dopamine (DA) and noradrenaline (NA) reuptake in central nervous system[35]. It contains various potentially active compounds. Hyperforin and Hypericin are thought to be its main constituents. In the present study St. John's Wort reduced the immobility time of rats in FST. Antidepressant effect of St. John's Wort in FST is due to an increase in monoaminergic neurotransmission resulting from MA reuptake inhibition[36], more potently in DA[37]. St. John's Wort also enhanced memory functions which is consistent with the previous reports[38,39]. It has been reported that it not only improved memory acquisition and memory consolidation, but almost completely reversed scopolamine induced amnesia[40-42]. However no effect on cognitive functions following St. John Worts administration was also reported[43]. In the present study we report that 2 weeks administration of St. John's Wort can improve memory functions which may be due to the changes in the content of monoamines in the brain.

A role of 5-HT in the pathogenesis of depression has been the subject of research interest over the past 30 years. Experimental evidence based primarily on the drug therapy suggests that enhancing serotonergic neurotransmission produces antidepressant effects. Serotonin hypothesis of depression was proposed based upon evidence that depleting 5-HT could cause depression while elevating them might have an antidepressant effect[44].

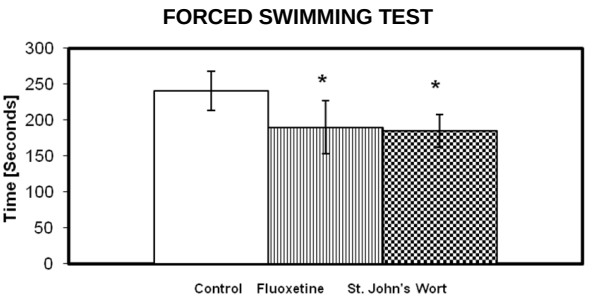

Figure 2: The effect of fluoxetine and St. John's Wort on immobility time of rats in forced swimming test. Values are means±S.D. (n=6). Significant difference by Newman-Keuls test: *p<0.05 vs control group following one way ANOVA.

This hypothesis was supported by the post mortem studies of 5-Hydroxyindoles performed in the brains of suicide victims and depressed patients have shown lowered 5-HT and 5-HIAA levels. Fluoxetine was the first antidepressant agent that acts by selectively inhibiting neuronal reuptake of 5-HT. It is known to have antidepressant activity and also known to enhance memory functions of rats by increasing serotonergic neurotransmission. Since a deficiency of 5-HT is reported in human depression therefore administration of SSRIs increase postsynaptic 5-HT function which induces antidepressant effect.

In the present study, fluoxetine is equally effective in inducing antidepressant like effect as herbal antidepressant St. John's Wort. Memory functions of rats was more enhanced following treatment with St. John's Wort as compared to fluoxetine. This may be due to the fact that SSRIs exerts its effect by blocking 5-HT reuptake system without appreciably affecting the DA and NA system[45] whereas St. John's Wort exerts its effect by reuptake inhibition of several neurotransmitters DA, 5-HT and NA[46]. 5-HT and DA both are the neurotransmitters that are involved in the enhancement of memory so therefore St. John's Wort is able to effectively enhance cognitive functions as well as induce antidepressant effect. Because of the rising cost of pharmaceutical antidepressants, the comparatively low cost and high efficacy of Hypericum perforatum extract makes it worthy of consideration in the economic evaluation of mild to moderate depression treatments.

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