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Original Research Article

A Comparative Study of Effects of Serotonergic Psychoactive Agents on Intestinal Motility

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Abstract

Background: In the current scenario, the increased prevalence of stress which leads to Depression, a mood disorder, is the most common illness worldwide. It has become a leading cause of disability, suicidal tendencies, and impairment in daily life, thus affecting about 350 million people globally. Deficiency or fluctuations in the levels of serotonin (5-HT), norepinephrine, and dopamine occur in depression. Pharmacotherapy i.e, antidepressants are the mainstay of treatment based on the monoaminergic hypothesis. In the present study, we explored the acute side effects of fluoxetine(SSRI) and amitriptyline (TCA) on contractility of the isolated ileal smooth muscle of rabbits in-vitro.

Methods: This in vitro study was carried out on isolated ileal muscle of six rabbits weighing 2 to 4.5 kg to explore the effect of fluoxetine and amitriptyline, for which Ach-mediated intestinal activity was taken as standard (control) in our study. The effect was seen on the amplitude of gut motility by using dale's organ bath. The ileal smooth muscle contractions were recorded by using Medicad Neuro Lab System.

Results: The mean ± standard deviation for Ach, Fluoxetine, and Amitriptyline were found as 8.00±2.75, 2.58±2.01, and 3.91±2.13 respectively. Fluoxetine and Amitriptyline decrease the amplitude of isolated ileal smooth muscle of rabbits.

Conclusion: Inability of fluoxetine to enhance serotonergic transmission in vitro and anti-muscarinic action of amitriptyline leads to a decrease in motility of isolated ileal smooth muscle.

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Introduction

Gut is the only organ that manifests integrated neuronal activity even after isolation from the central nervous system [1]. Gastrointestinal tract has its own independent nervous system, known as the enteric nervous system (ENS) [2]. ENS accomplishes muscle activity and mucosal functions because of complex integration of interneurons, motor neurons and neurons encoding stimuli [3]. The gastrointestinal motility is generated because of local and circulating neuro-humoral substances [4,5]. The rhythmic pattern of intestinal motility is because of the activity of slow waves

generated in the pacemaker cells of the intestine i.e Interstitial cells of Cajal [6]. Mucosal serotonin, 5-hydroxytryptamine (5-HT) can initiate peristaltic reflexes in the colon, recent studies have differed as to whether or not the role of mucosal 5-HT is critical [7]. We therefore tested the hypothesis that the secretion of 5-HT from mucosal enterochromaffin (EC) cells is essential for the manifestation of colonic peristaltic reflexes.

In current scenario, depression is a common illness worldwide, with an estimated 3.8% of the population affected, including 5.0% among adults and 5.7% among adults older than 60 years; approximately 280 million people in the world have depression [8]. Pharmacotherapy i.e., anti-depressants remain the mainstay of treatment based on the monoamine hypothesis [9]. The Monoamine theory proposes that, patients with depression have low levels of serotonin, norepinephrine, and dopamine [10,11]. All currently licensed antidepressants are believed to increase serotonin, norepinephrine or both in the synapse. The mechanisms to increase these neurotransmitters vary, though antidepressant drugs target reuptake by the nerve terminals [12].

Tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) both have classical mechanisms, while the selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed antidepressants [13]. SSRIs basically act by selectively inhibiting reuptake of serotonin (5-hydroxytryptamine) by blocking SERT. By blocking the reuptake of serotonin in the synaptic space they increase concentration of serotonin at post-synaptic nerve terminal membrane [14]. Amitriptyline belongs to the tricyclic antidepressant (TCA) medication class, and it works by preventing serotonin and norepinephrine neurotransmitter reuptake.

Methods

The study was conducted in Experimental Lab of Department of Physiology, BRD Medical College, for duration of 9 months on rabbits weighing 2 to 4.5 kg. The ileum part was used for the study. The availability of rabbits was done from registered breeder. The animals were housed in Animal House of BRD Medical College, Gorakhpur which has been registered with CPCSEA. The animals were procured and kept in animal house at optimum environmental condition for 1 week before the experiment. The animals were given standarized diet.

Before sacrificing, rabbits were starved overnight and then anesthetized by using enflurane. Dissection process was started by giving a midline incision and part of ileum which was located near the end of small intestine was dissected out by leaving a margin of 5cm.

This ileal part was placed in the petridish containing lukewarm tyrode solution bubbled with 100% O_2. Longitudinal segment of 1.5 cm of ileum was placed in an organ bath containing tyrode's solution maintained at 37± 1°C and continuously bubbled with 95% O_2 and 5% CO_2. The tissue segment was mounted vertically, the one end of which was fastened to a glass tube support and the other end fixed to a force transducer with an initial tension of 2 g. Isotonic contractions were amplified by bridge amplifier and digitalized via an analog / digital interface (Medicaid System Neuro Lab) to acquire onto a personal computer. The initial recordings of spontaneous contractions were made for 15 min without any external interventions. Then after achieving normal waveforms we add 1ml of acetylcholine Hydrochloride(10^{-6}M) into inner organ bath, the tracings were taken for 15 min and then we washed the gut preparation with tyrode's solution, again when normal waveforms were achieved, we add the drug i.e. 1ml of Fluoxetine 4.3µg/ml

($1.4x10^{-6}$M) ,the tracings were taken for 15 min. To proceed further, the washing of gut preparation with tyrode's was done to achieve normal tracings, to which the addition of another drug i.e. 1ml of Amitriptyline Hydrochloride 32µg/ml (10^{-6} M) was done and the tracings were taken for 15 min. The same procedure was done in each rabbit. The isotonic ileal smooth muscle activity was recorded through the displacement transducer. Data was obtained as mean±SD of amplitude of contractions. Data related to drugs used for study were compared using One-way analysis of Variance and p value <0.05 was considered statistically significant.

Results

Table 1: Showing Basal amplitude distribution of gut motility and after instillation of Acetylcholine HCl and fluoxetine

Serial no. of experiments	1	2	3	4	5	6	Mean±SD
Basal amplitude(mm)	3	4	4	6	9	7	5.50±2.25
Acetylcholine Hcl	6	6	5	10	12	9	8.00±2.75
Fluoxetine	1	1.5	1	2	6	4	2.58±2.01

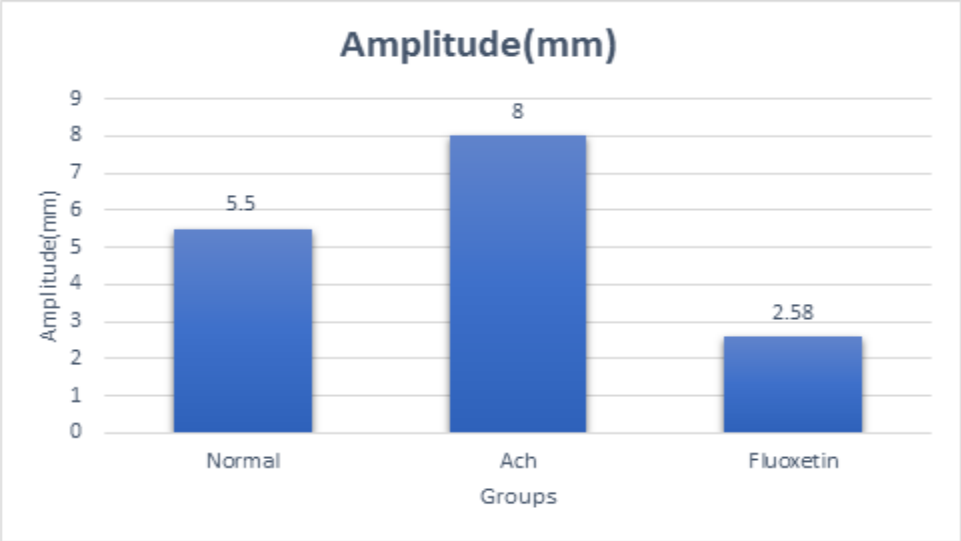

Figure 1: Basal amplitude distribution of gut motility and after instillation of Acetylcholine HCl and fluoxetine

Table 2: Basal amplitude distributions of gut motility and after instillation of Acetylcholine HCl and Amitriptyline HCl

Serial no. of experiments	1	2	3	4	5	6	Mean±SD
Basal amplitude (mm)	3	4	4	6	9	7	5.50±2.25
Acetylcholine HCl	6	6	5	10	12	9	8.00±2.75
Amitriptyline HCl	1.5	3	2.5	4	7.5	5	3.91±2.13

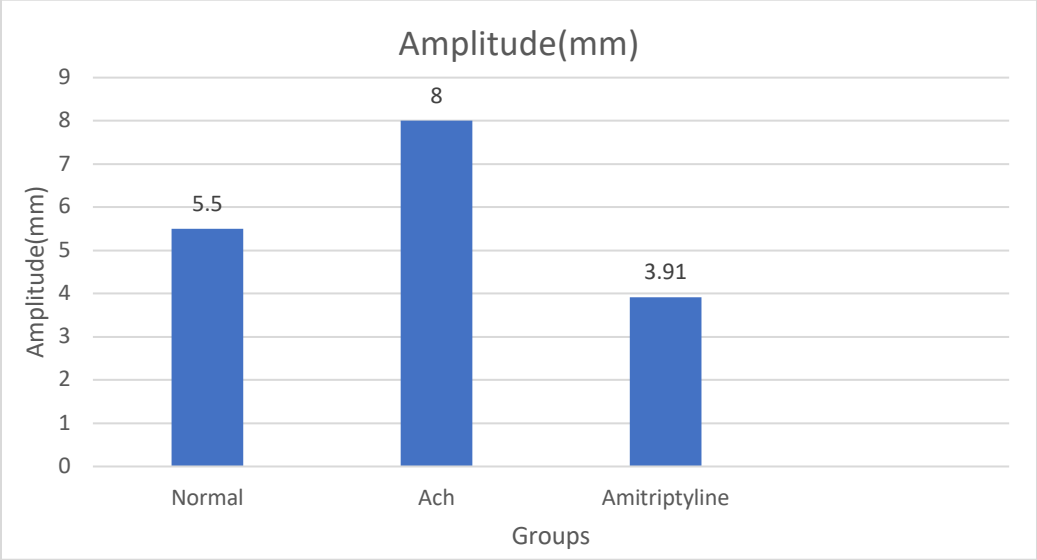

Figure 2: Basal amplitude distribution of gut motility and after instillation of Acetylcholine HCl and Amitriptyline HCl

Table 3: Basal amplitude distribution of gut motility and after instillation of fluoxetine and Amitriptyline HCl.

Serial no. of experiments	1	2	3	4	5	6	Mean±SD
Basal amplitude(mm)	3	4	4	6	9	7	5.50±2.25
Fluoxetine	1	1.5	1	2	6	4	2.58±2.01
Amitriptyline HCl	1.5	3	2.5	4	7.5	5	3.91±2.13

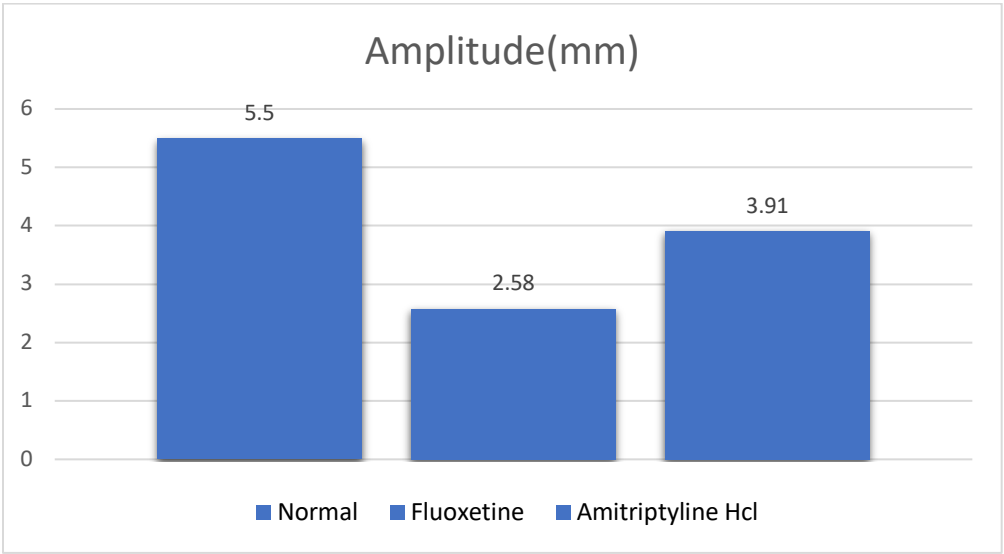

Figure 3: Basal amplitude distribution of gut motility and after instillation of Fluoxetine and Amitriptyline HCl

Table 1,2,3 and Figure 1,2, 3 summarizes the findings of the present study showing the acute effects of fluoxetine and amitriptyline on isolated ileal smooth muscles of rabbit which were measured in terms of amplitude of contractions by taking Ach mediated intestinal contractions as standard (control). Table 1 and figure 1 showing the comparison of amplitude of contraction between Ach (10^{-6}M) and

Fluoxetine(1.4x10 $^{-5}$M) as 8.00±2.75 and 2.58±2.01 respectively(p- value = 0.0045) which was statistically significant as p value is <0.05.

Table 2 and Figure 2 showing the comparison of amplitude of contraction between Ach (10 $^{-6}$M) and Amitriptyline Hydrochloride (10 $^{-6}$M) as 8.00±2.75 and 3.91±2.13 respectively (p value =0.006) which was statistically significant as p value is <0.05. Table 3 and Figure 3 showing the comparison of amplitude of contraction between Fluoxetine (1.4 ×10^{-5}) and Amitriptyline Hydrochloride (10^{-6}) as 2.58±2.01 and 3.91±2.13 respectively. The p-value is 0.092, which was not significant at p<0.05, but significant at p < 0.10. i.e. it was 90% significant.

Discussion

From the result of our study, it was observed that Fluoxetine and Amitriptyline Hydrochloride mediated ileal contractions decreases contractility (amplitude) of ileal smooth muscle on comparison with Ach (control), which shows significant p-value as 0.0045 and 0.006 respectively. Although many in vivo studies have been done but this current study was undertaken to observe the acute effects of fluoxetine and amitriptyline hydrochloride and to explore the possible mechanism on contractility of ileal smooth muscle of rabbit in vitro. A study conducted by Langton PD *et al*., (2018) [15] studied about the contractility of gastrointestinal muscle and the enteric nervous system in vitro along with the influence of acetylcholine on gastrointestinal motility. Thereby concluding that, acetylcholine increases the motility by acting on muscarinic receptors (M3).

Fluoxetine, an antidepressant belongs to SSRI's (Selective Serotonin Reuptake Inhibitor) group that selectively inhibit membrane associated serotonin transporter (SERT), act centrally and peripherally to enhance the availability of physiologically released 5-HT, leads to various side- effects [16]. Camilleri M [17] conducted a clinical trial on human subjects in which he found out that fluoxetine increases the motility of the gut due to its ability to inhibit SERT as manifested by decrease in orocecal transit time.

But in our study fluoxetine decreases the contractility which may be because of minimal ability of fluoxetine to block SERT in the isolated tissue, thereby decreasing the concentration of 5-HT in the serotonergic synapse [18]. In the isolated tissue, Fluoxetine may have a non-selective anticholinergic action as well which become more pronounced in the absence of enhanced serotonergic effect [19]. Serotonin, 5-HT has stimulating effect on the longitudinal muscle in the small intestine as it has a direct and an indirect component (neuronal release of acetylcholine contractions in the intestinal smooth muscle) on the gut musculature and also by acting on 5HT-2 and 5HT-4 receptors [20].

Amitriptyline, an antidepressant belonging to TCA (Tricyclic antidepressant) group blocks the reuptake of nor-epinephrine and serotonin. They are competitive antagonists at the muscarinic, histaminergic and alpha-1 and alpha-2 adrenergic receptors, which leads to its characteristic side effects. Because of anti- muscarinic action of amitriptyline, it decreases the motility of ileal smooth muscle [21].

Conclusion

To conclude this study, effect of Fluoxetine and Amitriptyline was studied in the isolated ileal muscle of rabbit. Depression, affecting majority of population can be treated by various methods but the most common among them is the use of antidepressants. The movement of gut shows the transmission of human emotions by brain areas. Contractions of muscles was recorded by organ bath system, the basal amplitude shows the comparative value when

compared with Acetylcholine HCl and shows the inability of fluoxetine to enhance serotonergic transmission and antimuscarinic action of amitriptyline leads to decrease in motility of isolated ileal smooth muscle in vitro.

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