International Journal of Pharmaceutical Development & Technology

e ISSN - 2248 - 910X

www.ijpdt.com

Print ISSN - 2248 - 9096

FENOTEROL BETA- AGONIST ON CONTRACTION AND RELAXATION OF INTESTINAL SMOOTH MUSCLE OF MALE ALBINO BALB-C MICE

Pooja Sharma* and Sushma Sharma

Department of Biosciences, Summerhill, Shimla, India.

ABSTRACT

The gastrointestinal tract is responsible for the absorption of nutrients and water into the body as well as the elimination of body waste. The small intestine is comprised of a long convoluted tube that is divided into the duodenum, jejunum, and ileum. Its functions consist of absorption of nutrients and water as well as retention and passage of waste materials. The movement of intestinal contents is dependent on the contraction of muscle fibers that are located throughout the intestinal wall. Absorption and movement of the contents are brought about by the activities of the absorptive cells of the mucosa and by coordinated contraction of the smooth muscle cells of the muscularis externa. The movements of the gut involve simultaneous contractions and relaxations of both circular and longitudinal smooth muscle layers at every point along its length. Mechanical recordings of physiological events can be traced back to the kymographic method. Keeping the above findings in view, the present study aims at understanding, whether already established dose of fenoterol, known to induce atrophic changes in muscles is likely to induce any toxic effects on other organ of vital importance or not. Hence, the experiment is designed in such a way to examine the undesirable toxic effects on smooth muscles.

Keywords: Beta –agonist, Fenoterol, Depolarization, Kymograph.

INTRODUCTION

Movement, the result of forces generated by the interaction of certain proteins, fueled by chemical energy, is a characteristic of all living cells. Muscle cells, with their specialized ability to generate force and motion, merely utilize an extension and modification of force generating apparatus common to all cells. Smooth muscles functions to propel substances along a definite tract, or pathway, within the body and are arranged in sheets or layers. Most often there are two layers, one running circularly and other longitudinally. When the two layers alternately contract and relax, they change the size and shape of the organ. Smooth muscle contraction is controlled by factors intrinsic to the muscle itself, by the autonomic nervous system, and by hormones; therefore, it is not normally under direct conscious control. Smooth muscle is under the control of autonomic nervous system. Nerve stimulation in smooth muscle causes membrane depolarization. Contractile response of many smooth muscles to several agonists is determined by the activation of the receptors associated with G-proteins that activate phospholipase C, releasing inositol P_3. Similarly, relaxation of smooth muscle cell can result from activation of receptors associated with G protein coupled to adenylcyclase, generation of cAMP and activation of cAMP dependent protein kinase [1]. Fenoterol treatment causes a small increase in fatigability due to decrease in oxidative metabolism with some cardiac hypertrophy [2].

Myometrial relaxation can be achieved by fenoterol at doses of 0.5 – 4 mg/min by continuous infusion. By the oral route, fenoterol 5mg (4-8 times daily), has been shown to be effective [3]. Fenoterol is a selective β_2-adrenoceptor agonist that has been in clinical use for decades. Fenoterol is more selective for β_2 adrenoceptors and its action is rapid [4, 5]. Peak plasma level generally occur within 20 to 90 minutes, however 75% of maximal effect is achieved within 5 minutes [4]. Fenoterol being stimulator of both β_1 and β_2 adrenoceptors is found to be more myotoxic. Comparison of dose dependent and haemodynamic effects of both the drugs revealed that each of these induce significant skeletal myocytes and cardiomyocytes death (0.03mM/kg). At this dose fenoterol induces a greater increase in heart rate, whereas clenbuterol has a greater hypotensive effect [6]. β_2 - adrenoceptors agonists such as fenoterol exert a number of well

Corresponding Author :- **Pooja Sharma** Email:- Sharma_poo.magic@rediffmail.com

characterized pharmacological effects in humans. Among these, more pronounced are bronchiodilation and relaxation of smooth muscle i.e intestine. In recent years much interest has been focused on the force generating apparatus responsible for the motility of intestinal epithelial brush border. Epithelia of rat intestine are shown to form fast microvillar movements [7]. In general, contraction is associated with increased intracellular Ca^{++} concentrations and relaxation is associated with decreased intracellular Ca^{++} concentrations. Ca^{++} normally runs into cells since extracellular concentration (10^{-3} M) is higher than resting intracellular concentration (10^{-7} M). Contraction in smooth muscle is driven by cyclic ATP driven interaction of myosin and actin. When cytosolic calcium increases and myosin binding sites on actin become available, an actomyosin complex is formed, followed by the sequential dissociation of Pi and ADP with conversion of myosin to its low-energy conformational state. These events are accompanied by simultaneous translocation of the attached thin filament toward the M line of the sarcomere. At the end of the power stroke, the actomyosin complex remains intact until ATP becomes available. ATP binding to myosin is a very exergonic reaction, with the result that ATP displaces actin from the myosin head. Thus, it is often said that ATP is required for muscle relaxation.

MATERIALS AND METHODS

Adult Swiss albino male mice of Balb- C strain weighing 25-30g were procured from Central Research Institute (CRI), Kasauli, Himachal Pradesh. They were housed in polypropylene cages under controlled conditions of temperature and light (24 ± 2^0C; 16 hr day light) and fed upon Hindustan lever pellet diet and water *ad libitum*. All experimental procedures were conducted after the approval of Institutional Animal ethics committee, Himachal Pradesh University (IAEC /BIO/4-2006), Shimla.

Mice were randomly assigned into two independent groups: One group containing normal mice served as control and the other group included mice as treated groups. Animals of second group were given daily oral administration of fenoterol (1.5 mg/ kg body wt) for 28 days).

Rate of membrane contraction and relaxation

It was done with the help of Kymograph apparatus as per the method of Rudolph Magnus [8]. After dissection small intestine free from adhering tissues, was removed from the Swiss albino male mice and set up for recording the isotonic relaxation in 20 ml jacketed organ bath containing Tyrode solution at 37^0C, continuously bubbled with air under 5mg of load , After an equilibrium period of at least 10-15 minutes , cumulative concentration effect curves for fenoterol (1.5 mg/kg body wt.) at 7, 14 , 21 and 28 days were obtained in smoked kymograph paper using a frontal writing lever of 5 times magnification. The values were statistically significant at all the stages in comparison to control ($P^* < 0.05$).

RESULTS

Intracellular potential of fat cells in the mice were measured in vitro. The effects of adrenergic agonists on these potentials were examined in an attempt to relate the electrical activity of the cells to the adrenergic induced stimulation of fat thermogenesis. Fenoterol did not depolarize the cells, although it stimulated thermogenesis in the tissues. The small intestine spontaneously produces a variety of motility patterns characterized as peristaltic or pendular, stationary or propagating, or twitch or segmental type. Several electrical signals have been shown to be associated with these different types of contractions, including slow waves, spikes or burst. The relationship between these different electrical signals and the patterns of contractions with which they are associated is not clear. It has been especially difficult to describe the relationship between the slow wave and the peristaltic reflex. For many years it has been known that the slow wave is able to propagate along the small intestine, and recently, the concept of propagation of peristaltic contractions has re-emerged.

Two main types of electrical activity (slow waves, corresponding to the basic electrical rhythm of the intestine, and spike potentials can readily be distinguished in the recordings obtained from kymograph.

Swiss albino male mice were divided in to two groups: a) control and b) fenoterol treated mice. Fenoterol induced contractile responses in the duodenum, jejunum and ileum were recorded on kymograph. There is relationship between intestinal inflammation, oxidative stress and contractility.

Duodenum

The rate of contraction was observed in the duodenum part of small intestine for 5 minutes. The number of contractions was found to be 53 in 5 minutes (Fig.1). The rate was calculated per minutes and was found to be 10.6, 21.2, 31.8, 42.4 contractions in 1, 2, 3, and 4 minutes.

After 7 days of fenoterol administration, the number of contractions gets increased and was found to be 100/5 minutes (Fig. 2). Rate was determined per minute and was calculated to be 20, 40, 60, 80 contractions in 1, 2, 3, and 4 minutes respectively. The percentage increase was found to be 88.6 % after drug treatment.

The number of contractions was found to be 62 in 5 minutes after 14 days of fenotrol administration (Fig. 3). The rate was calculated for 1, 2, 3, and 4 minutes and it was 12.4 contractions in 1 minute and 24.8 contractions in 2 minutes and 37.2 contractions in 3 minutes. The frequency of contractions was found to be 49.6 for 4 minutes. Little increase in the rate of contraction at day 14 when compared to 7 days stage of control duodenum was seen. And the percentage increase was found to be 16.98 %.

After drug treatment at 21 days stage, the rate of contraction was found to be 42 contractions in 5 minutes (Fig. 4). Little decrease (20.7%) in the rate of contraction was noticed when compared with control duodenum. At 28

days stage (Fig. 5), it was not possible to count the number of contractions in the duodenum part of small intestine after fenoterol administration.

Jejunum

The rate of jejunum contraction was found to be 46 contractions in 5 minutes (Fig. 6). The rate for 1, 2, 3 and for 4 minutes was found to be 9.2, 18.4, 27.6, 36.8 contractions.

After 7 days of drug treatment, the rate of contraction in the jejunum was found to be 65 contractions in 5 minutes (Fig.7). The rate of contraction in 1 minute was calculated to be 13 contractions and for 2 minutes it was found to be 26 contractions. The number of contractions for 3 and 4 minutes was calculated to be 39 and 52. The percentage increase in the rate of contraction when compared with the control jejunum was found to be 41.3 %.

Rate of contraction was further increased to 103 contractions in 5 minutes after 14 days of drug treatment (Fig.8). The rate was calculated for 1, 2, 3 and 4 minutes and was found to be 20.6, 41.2, 61.8 and 82.4 contractions. The percentage increase in the rate of contraction when compared with control jejunum was 123 %. Rate was found to be 56 contractions in 5 minutes. The percentage increase was found to be 21.7 %.

The contraction rate was 56 per 5 minutes at 21 days (Fig. 9), whereas the rate of contraction was found to be 45 in 5 minutes after 28 days of administration (Fig.10). It was 9, 18, 27, 36 contractions for 1, 2, 3 and 4 minutes. The percentage increase was found to be 2.1 %.

Ileum

The rate of contraction in the ileum of small intestine was calculated to be 107 in 5 minutes (Fig. 11). The rate was calculated for 1, 2, 3 and 4 minutes and it was found to be 21.4 contractions/ minute, and 42.8 contractions in 2 minutes, and 64.2 and 85.6 contractions in 3 and 4 minutes.

The rate of contraction get increased to 128 in 5 minutes after fenoterol treatment (Fig.12). The rate was determined for 1, 2, 3 and for 4 minutes and it was found to be 25.6, 51.2, 76.8 and 102.4 contractions. The percentage increase was found to be 19.6%.

At 14 days stage the rate of contraction was found to be 37 in 5 minutes (Fig.13). The rate was calculated for 1, 2, 3 and for 4 minutes. It was found to be 7.4 contractions/minute and 14.8 contractions in 2 minutes, 22.2 contractions in 3 minutes and 29.6 contractions in 4 minutes. The rate of contraction decreases in the ileum after 14 days of drug treatment.

The rate of contractions further get decreased to 4 contractions in 5 minutes after 21 days of fenoterol administration (Fig.14) and it was very less for 1 minute and was calculated to be 0.8 contractions/minute. It was 1.6, 2.4 and 3.2 contractions for 2, 3 and 4 minutes. It was not possible to calculate the number of contractions and rate of contraction at 28 days stage after drug treatment (Fig.15).

Relaxation rate of small intestine

Small intestine free from adhering tissues was removed from the Swiss albino male mice and set up for recording the isotonic relaxation in 20 ml jacketed organ bath containing Tyrode solution at 37^0C, continuously bubbled with air under 5 mg of load. After an equilibrium period of at least 10-15 minutes, cumulative concentration effect curves for fenoterol (1.5mg/kg body wt.) at 7, 14, 21 and 28 days were obtained in smoked kymograph paper using a frontal writing lever of 5 times magnification. Since fenoterol exhibited relaxant activity in this experiment.

The smooth muscle of the duodenum, jejunum and ileum, undergoes a biphasic mechanical response when exposed to fenoterol. The first phase, termed the phasic response, consisted of a rapid increase in tension which reached a sharp peak, followed by a rapid reduction in tension, which depended on an initial mobilization of intracellular calcium, probably from the sarcoplasmic reticulum, in an inositol triphosphate (IP3) dependent way. The second phase, the tonic response, consisted of a slower, more sustained increase in tension that is usually of a lesser magnitude. This response is more dependent on calcium from the extracelular medium and is due to an increased calcium influx across the membrane.

Duodenum

The rate of relaxation was calculated in the duodenum part of small intestine and was found to be 63 relaxations in 5 minutes. The rate of frequency was calculated for 1, 2, 3 and for 4 minutes and it was found to be 12.6, 25.2, 37.8 and 50.4 relaxations.

After 7 days of drug treatment, the rate was calculated to be 111 relaxations in 5 minutes and the percentage increase was found to be 76.1 %. The rate get further decreased to 56 relaxations in 5 minute after 14 days. The rate of relaxation frequency was calculated for 1, 2, 3, and 4 minutes. It was found to be 11.2, 22.4, 33.6 and 44.8 relaxations respectively. At 21 days stage the rate of relaxation was found to be 52 in 5 minutes. The percentage decrease was found to be 7.2%.The rate of relaxation cannot be calculated because it was not possible to count the number of relaxation peaks after 28 days of fenoterol treatment.

Jejunum

The frequency rate of relaxation for control jejunum was calculated to be 48 in 5 minutes. The rate was calculated for 1, 2, 3 and 4 minutes. It was calculated to be 9.6, 19.2, 28.8 and 38.4 relaxations respectively. The rate of relaxation was found to be 53 in 5 minutes after 7 days of drug treatment. The percentage increase was found to be 10.4%. Fenoterol administration after 14 days showed the rate of relaxation further increased to 87 in 5 minutes. The percentage increase was found to be 81.25%. Jejunum after 21 days of drug treatment exhibited decrease in the rate of relaxation and the decrease was found to be 29 relaxation in 5 minutes. The number of peaks of relaxation getting

decreased as the concentration of fenoterol increases from day 7 to day 21. The decrease in rate of relaxation was calculated for 1, 2, 3 and for 4 minutes. It was found to be 5.8, 11.6, 17.4 and 23.2 relaxations. The percentage decrease was found to be 39.5% when compared with the control jejunum. The of rate relaxation get decreased to 14 in 5 minutes after 28 days of drug treatment. The percentage decreased was found to be 70.8%.

Table 1. Rate of contraction/min in duodenum, jejunum and ileum of normal and drug treated mice at 7 days period

Rate of Contraction at 7 Days						
Tissues	**Time in minutes**	1	2	3	4	5
Duodenum	**Normal**	10.6	21.2	31.8	42.4	53.0
	Treated	20.0	40.0	60.0	80.0	100.0
Jejunum	**Normal**	9.2	18.4	27.6	36.8	46.0
	Treated	13.0	26.0	39.0	52.0	65.0
Ileum	**Normal**	21.4	42.8	64.2	85.6	107.0
	Treated	25.6	51.2	76.8	102.4	128.0

Table 2. Rate of contraction/min in duodenum, jejunum and ileum of normal and drug treated mice at 14 days period

Rate of Contraction at 14 Days						
Tissues	**Time in minutes**	1	2	3	4	5
Duodenum	**Normal**	10.6	21.2	31.8	42.4	53.0
	Treated	12.4	24.8	37.2	49.6	62.0
Jejunum	**Normal**	9.2	18.4	27.6	36.8	46.0
	Treated	20.6	41.2	61.8	82.4	103.0
Ileum	**Normal**	21.4	42.8	64.2	85.6	107.0
	Treated	7.4	14.8	22.2	29.6	37.0

Table 3. Rate of contraction/min in duodenum, jejunum and ileum of normal and drug treated mice at 21 days period

Rate of Contraction at 21 Days						
Tissues	**Time in minutes**	1	2	3	4	5
Duodenum	**Normal**	10.6	21.2	31.8	42.4	53.0
	Treated	8.4	16.8	25.2	33.6	42.0
Jejunum	**Normal**	9.2	18.4	27.6	36.8	46.0
	Treated	11.2	22.4	33.6	44.8	56.0
Ileum	**Normal**	21.4	42.8	64.2	85.6	107.0
	Treated	0.8	1.60	2.40	3.20	4.0

Table 4. Rate of contraction/min in duodenum, jejunum and ileum of normal and drug treated mice at 28 days period

Rate of Contraction at 28 Days						
Tissues	**Time in minutes**	1	2	3	4	5
Duodenum	**Normal**	10.6	21.2	31.8	42.4	53
	Treated	0.0	0.0	0.0	0.0	0.0
Jejunum	**Normal**	9.2	18.4	27.6	36.8	46.0
	Treated	9.0	18.0	27.0	36.0	45.0
Ileum	**Normal**	21.4	42.8	64.2	85.6	107.0
	Treated	0.0	0.0	0.0	0.0	0.0

Table 5. Rate of relaxation/min in duodenum, jejunum and ileum of normal and drug treated mice at 7 days period

Rate of Relaxation at 7 Days						
Tissues	**Time in minutes**	1	2	3	4	5
Duodenum	**Normal**	12.6	25.2	37.8	50.4	63.0
	Treated	22.2	44.4	66.6	88.8	11.0
Jejunum	**Normal**	9.6	19.2	28.8	38.4	48.0
	Treated	10.6	21.2	31.8	42.4	53.0
Ileum	**Normal**	20.0	40.0	60.0	80.0	100.0
	Treated	26.0	52.0	78.0	104.0	130.0

Table 6. Rate of relaxation/min in duodenum, jejunum and ileum of normal and drug treated mice at 14 days period

Rate of Relaxation at 14 Days						
Tissues	**Time in minutes**	1	2	3	4	5
Duodenum	**Normal**	12.6	25.2	37.8	50.4	63.0
	Treated	11.2	22.4	33.6	44.8	56.0
Jejunum	**Normal**	9.6	19.2	28.8	38.4	48.0
	Treated	17.4	34.8	52.2	69.6	87.0
Ileum	**Normal**	0.0	40.0	60.0	80.0	100.0
	Treated	4.0	8.0	12.0	16.0	20.0

Table 7. Rate of relaxation/min in duodenum, jejunum and ileum of normal and drug treated mice at 21 days period

Rate of Relaxation at 21 Days						
Tissues	**Time in minutes**	1	2	3	4	5
Duodenum	**Normal**	12.6	25.2	37.8	50.4	63.0
	Treated	10.4	20.8	31.2	41.6	52.0
Jejunum	**Normal**	9.6	19.2	28.8	38.4	48.0
	Treated	5.8	11.6	17.4	23.2	29.0
Ileum	**Normal**	20.0	40.0	60.0	80.0	100.0
	Treated	1.2	2.4	3.6	4.8	6.0

Table 8. Rate of relaxation/min in duodenum, jejunum and ileum of normal and drug treated mice at 28 days period

Rate of Relaxation at 28 Days						
Tissues	**Time in minutes**	1	2	3	4	5
Duodenum	**Normal**	12.6	25.2	37.8	50.4	63.0
	Treated	0.0	0.0	0.0	0.0	0.0
Jejunum	**Normal**	9.6	19.2	28.8	38.4	48.0
	Treated	2.8	5.6	8.4	11.2	14.0
Ileum	**Normal**	20.0	40.0	60.0	80.0	100.0
	Treated	0.0	0.0	0.0	0.0	0.0

Fig. 1.Rate of contraction/min in duodenum, jejunum and ileum of normal and drug treated mice at 7 days period.

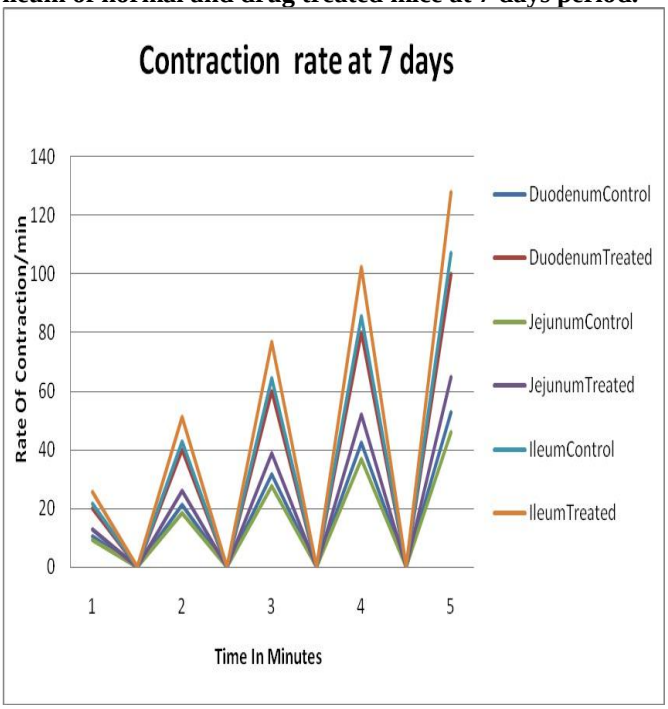


Fig 2. Rate of contraction/min in duodenum, jejunum and ileum of normal and drug treated mice at 14 days period

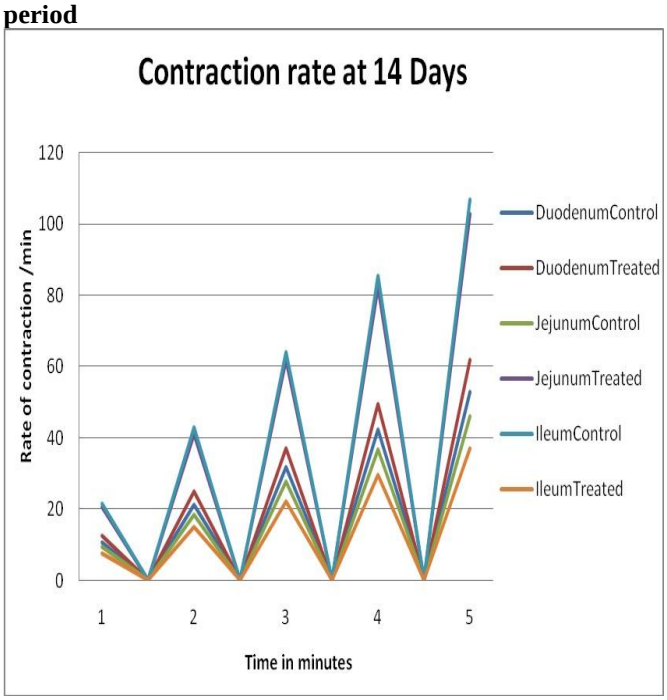


Fig 3. Rate of contraction/min in duodenum, jejunum and ileum of normal and drug treated mice at 21 days period

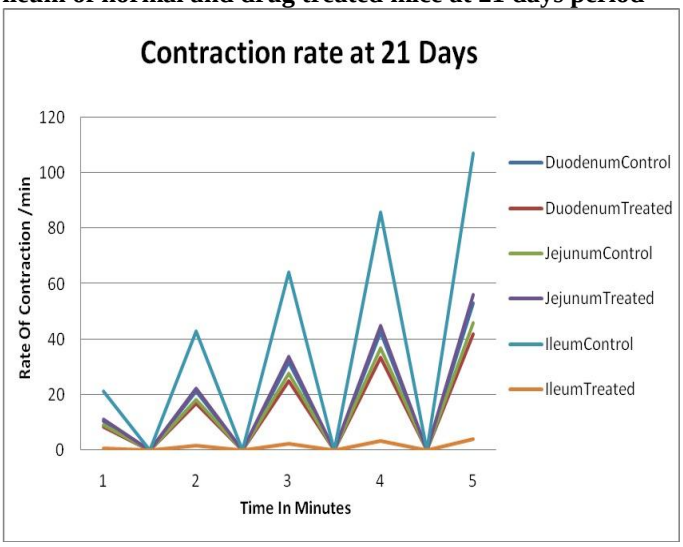


Fig 4. Rate of contraction/min in duodenum, jejunum and ileum of normal and drug treated mice at 28 days period

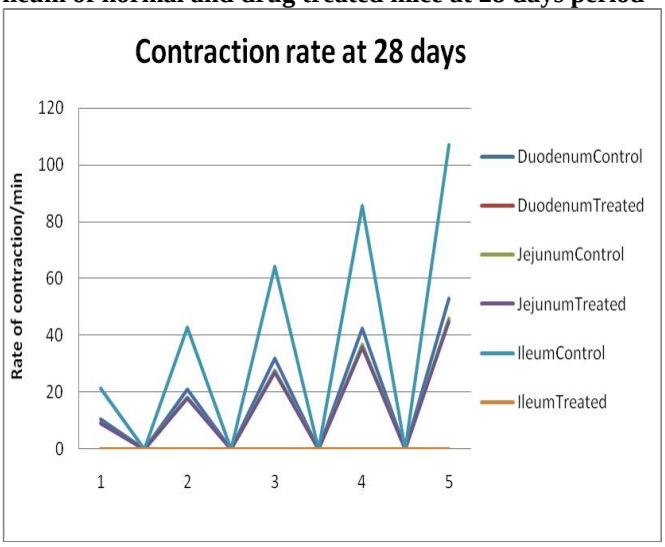


Fig 5. Rate of relaxation/min in duodenum, jejunum and ileum of normal and drug treated mice at 7 days period

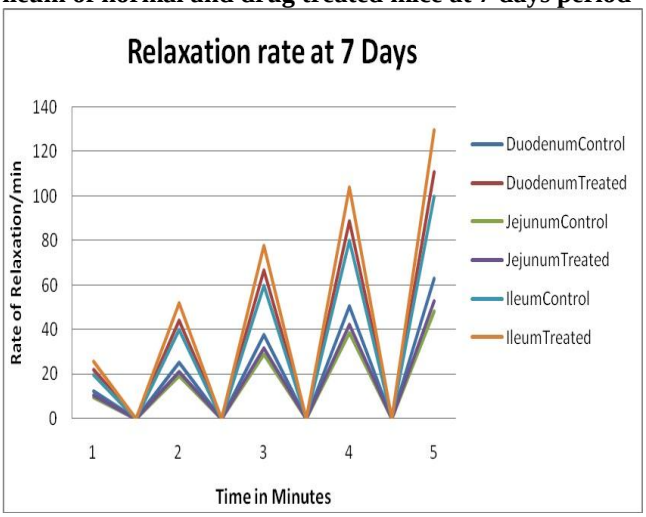


Fig 6. Rate of relaxation/min in duodenum, jejunum and ileum of normal and drug treated mice at 14 days period

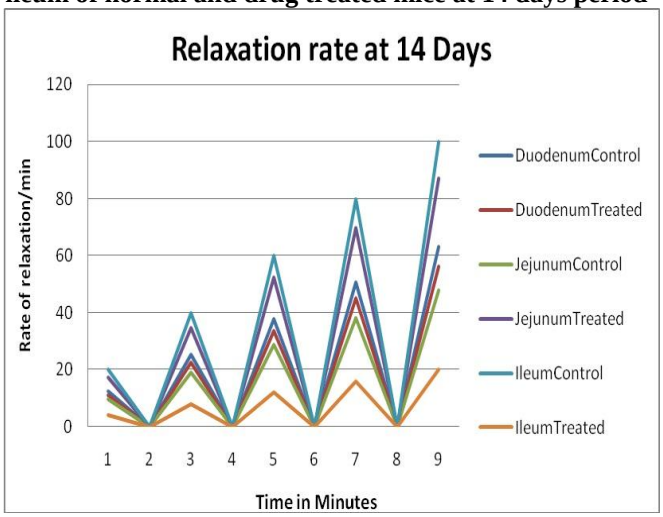


Fig 7. Rate of relaxation/min in duodenum, jejunum and ileum of normal and drug treated mice at 21 days period

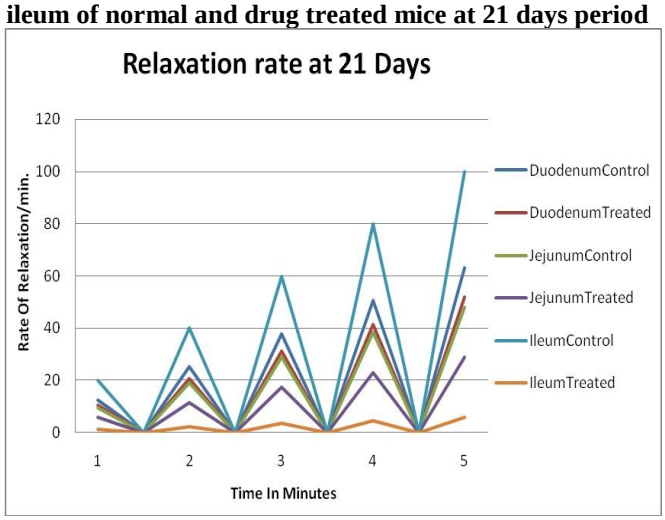
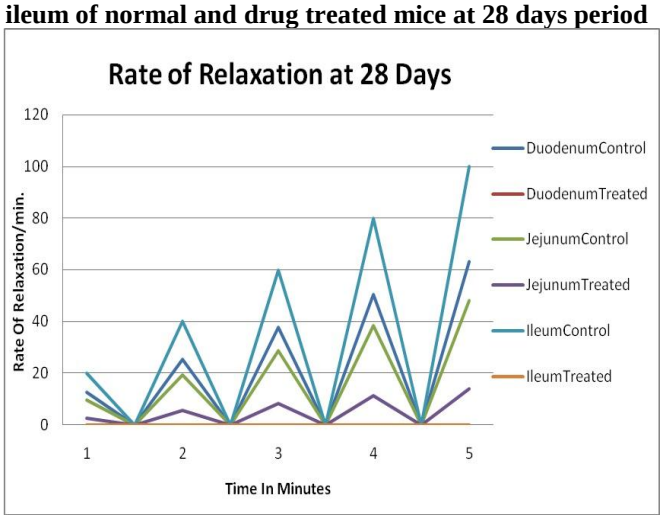


Fig 8. Rate of relaxation/min in duodenum, jejunum and ileum of normal and drug treated mice at 28 days period



Ileum

The rate of relaxation in the control ileum was calculated to be 100 relaxations in 5 minutes. The frequency of relaxation was also calculated for 1, 2, 3 and 4 minutes. It was calculated to be 20, 40, 60 and 80 relaxations. The relaxation rate after 7 days of drug treatment was found to be 130 in 5 minutes. The percentage increase was found to be 30%. The rate of relaxation was abruptly decreased to 20 in 5 minutes after 14 days of fenoterol treatment. Rate was calculated for 1, 2, 3 and for 4 minutes. It was found to be 4,8,12 and 16 relaxations. The percentage decrease was found to be 80%.The frequency of relaxation rate was found to be 6 in 5 minutes after 21 days of drug administration. Severe decline in the relaxation rate takes place as the concentration of fenoterol increases. The percentage decrease was found to be 94%. The muscle becomes totally relaxed after 28 days of drug administration. It was not possible to calculate the peaks of relaxation with respect to time.

DISCUSSION AND CONCLUSION

Smooth muscle cells lack the striated banding pattern found in cardiac and skeletal muscle, and they receive neural innervation from the autonomic nervous system. In addition, the contractile state of smooth muscle is controlled by hormones, autocrine/paracrine agents, and other local chemical signals. Smooth muscle cells also develop tonic and phasic contractions in response to changes in load or length. Regardless of the stimulus, smooth muscle cells use cross-bridge cycling between actin and myosin to develop force, and calcium ions (Ca^{2+}) serve to initiate contraction. The muscular system is the body's network of tissues for both conscious and unconscious movement. Movement is generated through the contraction and relaxation of specific muscles. Some muscles, like those in the arms and legs, are involved in voluntary movements such as raising a hand or flexing the foot. Other muscles are involuntary and function without conscious effort. Voluntary muscles include skeletal muscles and total about 650 in the whole human body. Skeletal muscles are controlled by the somatic nervous system whereas the autonomic nervous system controls involuntary muscles. Involuntary muscles include muscles that line internal organs. These smooth muscles are called visceral muscles, and they perform tasks not generally associated with voluntary activity throughout the body even when it is asleep.

The smooth muscle of digestive tract form part of visceral smooth muscle is syncytial in structure with well developed automatism. Spontaneous rhythmic contractions are frequently observed in visceral muscles. Their frequency and amplitude varied and may be modified by nerve impulses and their chemical mediators.The gastrointestinal system function to transfer organic nutrients, salt and water from the external environment to the internal environment, where they can be distributed to cells by the circulatory system. The small intestine has been generally regarded as major site of drug absorption after oral administration [9]. The length and weight of intestine has been used as a physiological parameter in the study of extent of absorption. Gradual increase in the length of the fenoterol treated mice was observed from 7 – 28 days of investigation.

Records of the intestinal length suggests that effect of beta – agonist fenoterol were expressed as early as in seven days and continue to demonstrate almost parallel changes throughout the period of investigation. It appears that splanchnic tissues like gastrointestinal tract largely compete with other body tissues for nutrients from the same arterial blood pool [10]. Visceral smooth muscle contraction occurs spontaneously, meaning that muscle cell action potentials are generated without input from either the motor or autonomic nervous system. The muscle cells undergo rhythmic oscillations in membrane potential which, occasionally, reach the threshold of an action potential, and, thus, generate a spike. The action potential spreads via gap junctions from muscle cell to muscle cell, initiating a wave of muscle contraction in its wake. Visceral smooth muscle cells also exhibit muscle tonus, a state of long-term, steady contraction. The tonus is variable, depending on the number of muscle cells that participate. The rhythmicity and tonus inherent in the intestinal smooth muscle may be enhanced or suppressed by two nerve plexuses found between the layers of muscle and mucosa (Auerbach's and Meissner's plexuses) known as the enteric nervous system of the gut, the activity of the plexuses can be modified by the autonomic nervous system. When a piece of intestine is removed for study, the plexuses remain viable and can be stimulated or inhibited using parasympathomimetic or sympathomimetic drugs.

In vivo, myoelectric activity is altered [11] and the rate of intestinal transit is increased [12], which might be viewed as an extension of the immune response. In vitro, contractility of the smooth muscle is increased [13] and the function of certain enteric nerves is depressed [14]. In addition, the thickness of the muscle layers is increased due to both hypertrophy and hyperplasia, which may additionally alter gastrointestinal motility, since increased smooth muscle mass may exacerbate muscle contraction and amplify the effect of excitatory stimuli[15]. Changes in propulsive intestinal activity were also observed in dener-vated gut segments, suggesting that elements intrinsic to the intestinal wall, i.e, enteric nerves and smooth muscle cells, play a crucial role [16]. Specific changes have also been reported in contractility, which were not related to the responses to depolarizing agents but to specific agonists, such as motilin and acetylcholine [17]**.** Additionally, intestinal inflammation may result in an increase in actin synthesis in smooth muscle, so we cannot exclude that some of the changes observed could result from increased contractile protein content [18]**.**

Physiological studies have detected age-related deterioration of muscle contractility in both intact and permeabilized muscle; the latter, which lacks the membrane-bound excitation contraction coupling system and soluble proteins involved in energy metabolism, offers

more direct information on contractile proteins. Studies on permeabilized muscle from several strains of rats showed that the two principal contractile parameters, specific force (P0, force divided by cross-sectional area) and unloaded shortening velocity (V0), generally decrease progressively with the animal's age [19]**.** In this context, the inhibitory effect of fenoterol could be caused by a reduction of calcium influx by way of calcium channels and/or through inhibition of calcium release from intracellular stores, decreasing the calcium concentration available for contractile machinery. However, these hypotheses require further studies. To the best of our knowledge, this is the first study to demonstrate the relaxant properties of these drugs.

The result of this study showed that the fenoterol produced contractile responses in small intestine of mice at bath temperature of 37^{o}C. Similar findings have been reported in *Gallus domesticus* caecal segments [20]. Concentration-dependent contractions of pulmonary artery or vein and bronchial artery of cattle to carbachol, histamine, and serotonin have also been demonstrated by [21]**.**

The contractions of the duodenal segments by carbachol are believed to be achieved through the muscarinic receptors [22], while the histamine effect observed is obtained by stimulation of H1 receptors present in duodenal smooth muscles [23]**.** Histamine (P-imidazolyl-ethylamine) is a powerful and consistent stimulant of smooth muscles [24, 25]. It is also a powerful gastric secretagogue [26] and induces the contraction of the smooth muscle of the gastrointestinal tract. In the intestinal longitudinal muscle of chicks, histamine is known to produce relaxations and appear to result from the release of adrenaline or noradrenaline [27]**.**

The receptors mediating the action of agonists, such as histamine and carbachol and fenoterol are known to be widely distributed in the gastrointestinal system, including the duodenum, [28]**.** However, changes in receptor population and responsiveness of tissues to agonists are known to occur in some diseased conditions [29, 30, 31].

To conclude, advancing our knowledge of control systems of gut motility does not require the creation of simplified models but it requires increased efforts to understand all the different components separately and in combination. Advanced imaging techniques; advanced motor assessments in vivo; advanced molecular techniques; detailed electrophysiology employed in vivo, in vitro, and in situ; and the creation of all encompassing models will create the enthusiasm and creativity needed to solve the fascinating control mechanisms of gastrointestinal motor activity and provide solutions for the dramatic presence of motility disorders. Finally, we emphasize the importance of fenoterol in motility studies. We also stress the importance of collaboration and a multidisciplinary approach for future understanding of the mechanisms of the small intestine in health and diseases.

REFERENCES

1. Alexander APH, Mathie A and Peters JA. Guide to receptors and channels. *Br J Pharmacol*, 41, 2004, 111-S126.
2. Ryall JG, David R, Gregorevic PP, Sillence MN and Lynch GS. β_2 – agonist administration reverses muscle wasting and improves muscle function in aged rats. *J Physiol*, 2004, 555, 175-188.
3. Dudenhausen JW, Hermer M and Rominger KL. Mutterliche plasmakonzeentrationen being multipler oraler fenoterol behandling. *Geburtsh Frauenheilk*, 49, 1989, 234-236.
4. Nelson HS. Beta - adrenergic therapy. *In, Allergy principles and practice.* (Eds. C.E. Middleton, R.C Reed and E.F Ellis). St. Louis, CV Mosby Co, 1988, pp. 647-664.
5. Jenne JW and Tashkin DP. Beta - adrenergic agonists. *In, Bronchial asthma-mechanisms and therapeutics.* (Eds. E.B. Weiss and M. Stein). Boston, Little, Brown and Co.1, 1993, 746-83.
6. Patiyal SN and Sharma S. Chronic oral administration of beta – adrenoceptor agonist clenbuterol affects myosin heavy chain (MHC) expression in adult mouse heart. *Physiol Res*, 2007, 56, 275-283.
7. Sandstrom B. A contribution to the concept of brush border function observation on intestinal epithelium in tissue culture. *Cytobiolope*, 3, 1971, 293-297.
8. Rudolph M. *In, Fundamentals of experimental pharmacology.* Hilton and company, *College Street Kolkata. 1904*, pp.102.
9. Young M, Choi W and Chiou L. Comparision of in vivo and postmortem small intestinal lengths of rats' implications in absorption prediction. *Biopharm & Drug Dis*. 1997, 18, 271-275.
10. Drackley JK, Donkin SS and Reynolds CK. Major advances in fundamental dairy cattle nutrition. *J Dairy Sci*, 89, 2006, 1324-1336.
11. Palmer JM, Weisbrodt NW, Castro GA. Trichinella spiralis, intestinal myoelectric activity during enteric infection in the rat. *Exp Parasitol*, 1984, 57, 132-141.
12. Castro GA, Badial – Aceves F, Smith JW, Dudrick S and Weisbrodt NW. Altered small bowel propulsion associated with parasitism. *Gastroentero*, 71, 1976, 620-625.
13. Vermillion DL and Collins SM. Increased responsiveness of Jejunal longitudinal muscle in Trichinella-infected rats. *Am J Physiol*, 254, 1988, G124-129.
14. Collins SM, Blennerhassett PA, Blennerhassett MG, Vermillion DL. Impaired acetylcholine release from the myenteric plexus of Trichinella-infected rats. *Am J Physiol*, 257, 1989, G898-903.

15. Alizadeh H, Castro GA and Weems WA. Intrinsic Jejunal propulsion in the guinea pig during parasitism with Trichinella spiralis. *Gastroenterol*, 9, 1987, 784-790.
16. Depoortere I, Van Assche G, Thijs T, Geboes K and Peeters T. Differential changes in Ach-, motilin-, substance P, and K^+-induced contractility in rabbit colitis. *Am J Physiol.*, 277, 1999, 61-80.
17. Weisbrodt NW, Lai M, Bowers RL, Harari Y and Castro GA. Structural and molecular changes in spiralis infection. *Am. J. Physiol*, 1994, 266, G856-62.
18. Ewa Prochniewiez A, La Dora V, Thompson B and David D. Age related decline in actomyosin structure and function. *Exp Gerontol*, 9, 2007, 684-690.
19. Ameh FA, OnyeyilI PA and Arowolo RA. Acetylcholine receptors in the caecum of domestic chickens. *J Vet Me*, 49, 1994, 131-132.
20. Arowolo RO and Eyre AP. Pharmacological comparison of isolated bronchial artery and pulmonary vein, possible functional relationship. *Comm Chem Pathol Pharmacol*, 26, 1979, 227-241.
21. Bolton J E and Field N. Calcium tonophone stimulated ion secretion in rabbit ilial mucosa in relation to active cyclic 3', 5'-AMP and carbylcholine. *J Memb Biol*, 1977, 35, 159.
22. Eyre P and Chand N. Preliminary evidence for two subclass of H_2 receptors. *Agent* & *Action*, 1979, 9, 1-3.
23. Gaddum JH and Picarelli ZP. Two kinds of tryptamine receptors. *Br J Pharmacol*, 12, 1957, 323-328.
24. Eghianruwa KI. A dictionary of Pharmacology and Toxicology. Stirling - Horden Publishers, Nigeria *Limited, Ibadan, Nigeria*, 2002, 62-157.
25. Ganong W F. Review of Medical Physiology, 19th Ed. Appleton and Lange, a Simon and Cluster, USA. 1999, 472.
26. Everett S D and Mann S P, Catecholamine release by histamine from the isolated intestine of the chick. *Euro J Pharmacol*, 1, 1967, 310-320.
27. Laurence D R, Bennett PN and Brown MJ. Clinical Pharmacology, 8th Edn., Churchill Livingstone, London,1997, 402.
28. Schrrurs AJM, Terpstra GK, Rajamakers JAM and Njkamp FP**.** Effects of vaccination with Haemophilis influenzae on adrenoreceptor function of tracheal and pharyngeal strips. *J Pharmacol Exp Ther*, 1980, 215, 691-696.
29. Veenedal GH, Kool DJ and Nij-Kamp FP. Influence of bordetella pertussis and its components on the endotoxins induced loss of beta adrenoreceptors binding site in guinea pig lungs. Proceeding of the Congress of European Society of Veterinary Pharmacology, Ghent, Belgium, 1985, 97.
30. Dina A O H and Arowolo AOR. The pharmacological receptors for histamine, serotonin and carbachol in the ileum of trypanosome brucei brucei infected guinea pigs. *Zariya Vet*, 4, 1989, 47-51.
31. Jibike GI, Onyeyili PA and Aku C E. The effect of trypanosome infection on the response of rabbit jejunal segments to histamine, carbachol and serotonin. *Trop Vet*, 12, 1994, 194-201.