INHIBITION OF PERISTALSIS IN GUINEA-PIG ILEUM
BY STEROIDS AND ALLIED SUBSTANCES

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Many workers have shown that certain steroids inhibit the contraction of different smooth muscles produced by various spasmogens. The effect of different steroids on the contractions produced by physiological method of stimulating the intestine by raising the intraluminal pressure was studied. The method followed was that of Trendelenburg for recording peristalsis in guineapig ileum. It has been shown that all the steroid derivatives caused inhibition of peristalsis. Quantitatively stilbestrol and ouabain were most potent followed by ethisterone, cortisone, sodium taurocholate and vitamin D. Stilbestrol has been shown to cause blockade of the superior cervical ganglia. It has been suggested that the steroid nucleus is responsible for their inhibitory action on peristalsis and this action is brought about by a direct effect on the plain muscle as well as by ganglionic blockade.

Many workers have shown that certain steroids inhibit the contraction of different smooth muscles produced by various spasmogens. The inhibition of acetylcholine contraction of the cats intestine in vitro by selected steroids has been shown by Toth et al. (1954). Bass et al. (1959) have shown that cortisone prevents the contraction of isolated guineapig ileum produced by pilocarpine. A detailed study of the effects of different steroid derivatives on the contraction of different smooth muscles caused by many spasmodic drugs has been done by Bass et al. (1960). They have shown that oestradiol, testosterone, progesterone, cortisone etc inhibit the contractions of the guineapig's ileum, tracheal muscle and uterus caused by pilocarpine, histamine and barium. They believed that this inhibitory action was not a non-specific effect, as it was reversible and that varying doses of the steroids were needed to inhibit the contractions produced by different spasmodic drugs. All these studies were done when the muscle was made to contract by using spasmogens. We were interested in finding out how the contractions produced by physiological method of stimulating the intestine, that is, by raising the intraluminal pressure would be affected. Therefore, the effect of various steroids on the peristaltic activity of guineapig's ileum was studied.

METHODS

Peristalsis in guineapig's ileum.—Trendelenburg's method was followed for recording peristaltic activity in guineapig's ileum with slight modifications,
In place of Mariotte bottle a reservoir of 100 ml capacity was used because it was observed that when Mariotte bottle was used the intestine got fatigued within a short period. With a smaller reservoir the intestine worked for many hours without fatigue. Peristalsis as well as longitudinal movements were recorded on a smoked drum.

The reservoir was slowly raised and the loop started filling and a critical pressure the peristaltic waves arose at the closed end and traveled down the loop pushing its contents into the pressure tubing. These changes in the internal volume were recorded by a piston recorder and were due to the activity of the circular muscle as shown in the upper part of the Fig. 1. Simultaneously changes in the length of the loop were recorded by a frontal writing lever as shown in the lower part of the Fig. 1. Peristalsis was allowed to continue for two mins and then the reservoir was lowered for 3 cm so that the lumen of the loop was no longer distended and the peristalsis stopped. For noting the effect of drugs, they were kept in the bath for two mins and then the reservoir was raised to get peristalsis for 2 mins. After two mins the drug was washed and recovery was seen within two mins. The drugs and their doses are shown in Table 1. All the steroids were dissolved in alcohol except ouabain which was given in aqueous solution and testosterone given as aqueous suspension. Volume of injection did not exceed 0.1 ml.

**TABLE I**

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Dose μg/ml for partial depression of peristalsis</th>
<th>Approximate potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stilbestrol</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Ouabain</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Ethisterone</td>
<td>20</td>
<td>1/20</td>
</tr>
<tr>
<td>Cortisone</td>
<td>50</td>
<td>1/50</td>
</tr>
<tr>
<td>Sodium taurocholate</td>
<td>250</td>
<td>1/150</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>800</td>
<td>1/800</td>
</tr>
</tbody>
</table>

Longitudinal movements of guinea pig small intestine.—The method followed was described by Burn (1952). The contractions were recorded on the smoked drum. After recording the normal contractions with acetylcholine and nicotine the steroid was put in the bath and kept for 2 mins and then the effects of the same doses of acetylcholine and nicotine were observed in the presence of the steroid.
Nictitating membrane of the cat.—The method followed is that described by Burn (1952). Cats were anaesthetised with chloralose (80 mg/kg) after induction with ether. Blood pressure was recorded from the left carotid artery by mercury manometer. Sympathetic nerve was isolated on the right side and on the same side the contractions of nictitating membrane were recorded on the smoked drum. Preganglionic fibers of the superior cervical ganglia were stimulated by induction shocks for one min every two mins. Drugs were given by a retrograde injections through the lingual artery or intracarotid injections. The contractions of the nictitating membrane were recorded immediately after the administration of the drug as well as after every two mins till the recovery was complete. The effect of adrenaline (10 ug) was also seen before and after the administration of the steroid.

RESULTS

Peristalsis in guineapig's ileum.—All the steroids caused inhibition of the peristalsis in the guineapig's ileum. The various doses of the steroids were added to the bath dissolved in 0.1 ml of alcohol. It was observed that alcohol in the doses of 0.1 to 0.4 ml in 100 ml bath did not cause any inhibition of the peristalsis. On the basis of the doses required to cause partial inhibition of the peristalsis, stilbestrol and ouabain were the most potent followed by testosterone, ethisterone, cortisone, sodium taurocholate and vitamin D respectively. These drugs also inhibited the longitudinal movements. Ouabain, sodium taurocholate and vitamin D though decreased the longitudinal movements yet at the same time increased the tone of the longitudinal muscle. The doses in which they caused inhibition of peristalsis are shown in Table 1 and the effect is shown in Figs. 1 and 2.

Fig. 1. Effect of stilbestrol on peristalsis and longitudinal movements of guineapig's ileum.
The method followed is that described in the text.
Nictitating membrane of the cat.—In one experiment injection of 50 µg of stilbestrol in 0.05 ml of alcohol through lingual artery caused complete depression of the response of nictitating membrane to electrical stimulation of the preganglionic sympathetic fibers. Alcohol (0.05 ml) did not affect the response of nictitating membrane to stimulation. Intracarotid injection of 300 µg of stilbestrol in 0.3 ml of alcohol completely abolished the response of the nictitating membrane to stimulation. Alcohol (0.3 ml) caused partial depression of the nictitating membrane. The response of the nictitating membrane to the intravenous injection of 10 µg of adrenaline was not altered by intracarotid injection of 300 µg of stilbestrol. The effect is shown in Fig. 4.

**Fig 4.** Effect of stilbestrol on the contractions of the nictitating membrane of cat produced by electrical stimulation of preganglionic nerve fibres of superior cervical ganglia and adrenaline. A, adrenaline; S, electrical stimulation of preganglionic fibers; St, stilbestrol.

**DISCUSSION**

It is clear that all these drugs produce inhibition of peristalsis. It is interesting to observe that these drugs though having different pharmacological properties and uses, show qualitatively similar response as far as peristalsis is concerned. The only common feature amongst these drugs is the steroid nucleus. Therefore, one is inclined to believe that this action is due to their chemical similarity. This type of similarity among the steroids has also been demonstrated in their inhibitory effect on the action of spasmodic drugs on smooth muscle (Bass et al., 1960). Though strictly speaking stilbestrol does not have a steroid nucleus but if one considers the spatial molecular configuration of stilbestrol then it can be considered as having a steroid nucleus. However, there is a qualitative difference in the action of stilbestrol, testosterone, ethisterone, cortisol on one hand and ouabain, sodium taurocholate and vitamin D on the other. The former four drugs produce
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inhibition of peristalsis as well as that of the longitudinal muscle while the last three drugs, though producing inhibition of peristalsis increase the tone of the longitudinal muscle. Quantitatively on the basis of the dose required to cause partial inhibition of peristalsis, stilbestrol and ouabain are most potent followed by testosterone, ethisterone, cortisone, sodium taurocholate and vitamin D respectively.

The interesting question arises as to how do these drugs produce inhibition of peristalsis. These drugs could be producing their inhibitory effect by acting directly on the smooth muscle or on the ganglia present in the gut. It is well known that various ganglionic blocking agents and local anaesthetics inhibit the peristalsis by blocking the ganglia. Feldberg and Lin (1949) has suggested that if the action of nicotine on an isolated piece of ileum is blocked by the drug and that of acetylcholine is left untouched then the drug is acting on the nervous mechanism. This method could not be applied because the action of both nicotine and acetylcholine is blocked by the steroids.

Bass et al., (1960) have shown that steroids inhibit drug induced contractions in the intestine. This action of steroids would be expected to inhibit the contractions produced by raising the intraluminal pressure. However, it was observed that the gut still responded to acetylcholine even though it failed to contract in response to raised intra luminal pressure in the presence of steroids. This suggested that the ganglionic blockade may be playing a possible role in the action of steroids in addition to their action on the smooth muscle.

The ganglionic blocking action of stilbestrol was seen on the nictitating membrane following the stimulation of preganglionic fibers of superior cervical ganglia. It was observed that 300 μg of stilbestrol in 0.3 ml of alcohol by intracarotid injection caused complete inhibition of the contraction of nictitating membrane to stimulation of the preganglionic fibers of superior cervical ganglia. Alcohol (0.3 ml) when injected in the same way causes only slight depression of the nictitating membrane. It was interesting to note that the response of the nictitating membrane to 10 μg of adrenaline intravenously was same before and after the intracarotid administration of 300 μg of stilbestrol. Thus the drugs do not have any adrenergic blocking action but only ganglionic blocking activity. It appears that the mechanism of action of stilbestrol in causing inhibition of peristalsis is by blocking the ganglia in the intestine and also by inhibition of the smooth muscle response.
REFERENCES


