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# ACTION OF SYMPATHOMIMETIC DRUGS ON THE ISOLATED JUNCTION OF THE BILE DUCT AND DUODENUM

BY

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The actions of adrenaline, noradrenaline and phenylephrine were studied both on the terminal tract of bile duct (prepared as spiral strips or intact) and on the adjacent duodenum taken from the calf and the cat. These amines contract the terminal bile duct and relax the duodenum. Furthermore, on the basis of the action of some adrenaline antagonists, the hypothesis is advanced that there are $\alpha$-receptors which mediate contraction of muscle in the sphincterial zone of the bile duct.

The way in which sympathomimetic drugs act at the junction of the bile duct and the duodenum is uncertain, principally because of the complications introduced by the deep embedding of the terminal part of the bile duct in the duodenum. In fact, neither the anatomical nor the physiological relationship between the terminal bile duct and the duodenum have been completely resolved. The results obtained by various workers with sympathomimetic drugs have been discordant, because of the difficulties encountered and because different techniques and different animal species have been used. Thus, there are many observations that adrenaline, like parasympathomimetic drugs, contracts the sphincter of Oddi (McWhorther, 1921 ; Lueth, 1931 ; Doubilet & Colp, 1937 ; Magee, 1946 ; Poilleux, Goidin & Nicolaidis, 1952 ; Erdmann & Henne, 1953 ; Taccani & Zaffagnini, 1953 ; Fogliatti, Ciocatto, Cattaneo & Giudice, 1954 ; Granser, Hertting, Rissel & Wewalka, 1956 ; Menguy, Hallenberck, Bollmann & Grindlay, 1958). Magee (1946) and Crema & Benzi (1961) have observed that spiral strips of bile duct contract in response to both sympathomimetic and parasympathomimetic drugs. Crema & Benzi (1961) found that this response, which varied from species to species, was independent of: (1) whether the strips were cut spirally, longitudinally, or transversely ; (2) whether the tract had or had not been embedded in the duodenal wall ; and (3) the degree of muscular tone preceding the application of the sympathomimetic drugs.

The effects of some sympathomimetic drugs have now been observed on the isolated terminal tract of the bile duct after separating it as far as possible from the duodenum.

## METHODS

### *Spiral strip of bile duct*

In one series of experiments the terminal tract of the bile duct from calves was isolated from the duodenum and cut into a spiral strip, as described by Crema & Benzi (1961). This preparation allows records of the responses of the circularly arranged smooth muscle.

*Intact bile duct*

In another series of experiments the terminal tract of the bile duct was isolated from the duodenum of calves and cats. Recordings were made of the flow of Tyrode solution through the duct and of the length of the tubular segment, that is of the responses of the longitudinal musculature (Benzi & Crema, 1961).

The isolated organs were immersed in oxygenated Tyrode solution at 37° C. To record the lengths of both the spiral strip and the longitudinal musculature of the sphincter, the writing lever exerted a force of 0.5 g on the tissue and the amplification was about 12 times. In several experiments longitudinal and circular strips of the duodenum adjacent to the bile duct were also studied.

Tissues from the calf were chosen because of the relative ease with which the muscle layers of the duodenum could be separated from those of the bile duct; from the cat, because of the anatomical similarity of its biliary tracts to those of man.

The sympathomimetic drugs tested were adrenaline hydrochloride, noradrenaline bitartrate, phenylephrine hydrochloride and isoprenaline hydrochloride. The concentrations of these drugs are expressed in terms of the bases.

A total of seventy calves and twenty-two cats were used.

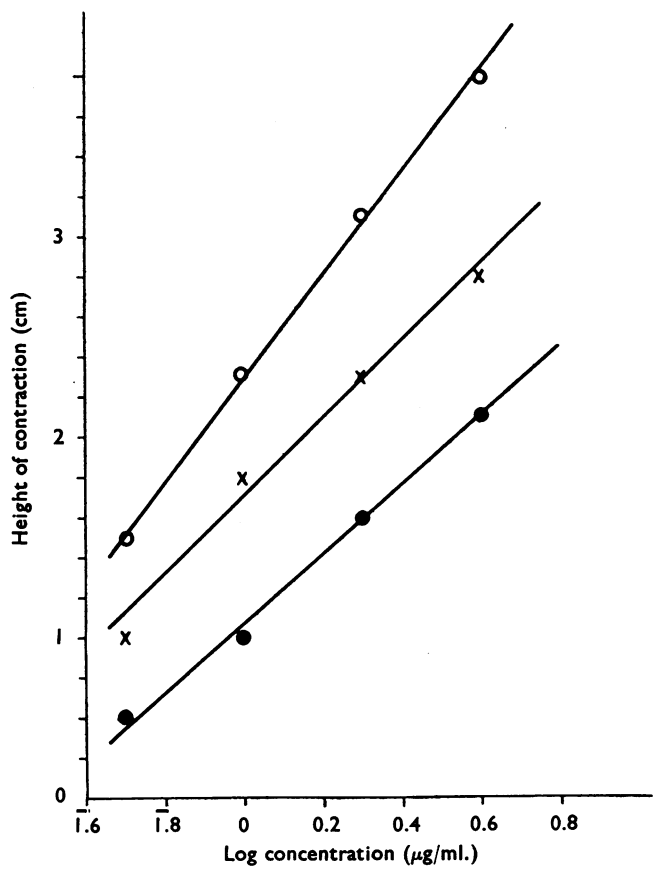


Fig. 1. Log concentration/response curves for adrenaline (○), noradrenaline (×) and phenylephrine (●), for the spiral strip of calf's terminal bile duct. Contractions are expressed as heights in cm on the kymograph record.

## RESULTS

### *Spiral strip of bile duct*

Fig. 1 shows dose/response curves for adrenaline, noradrenaline and phenylephrine. Adrenaline is the most potent drug in contracting the spiral strips, followed by noradrenaline. However, the contractions produced by phenylephrine lasted longer than those by adrenaline (Fig. 2) or by noradrenaline. Isoprenaline had no observed action in concentrations from 0.01 $\mu$g/ml. to 2 $\mu$g/ml. (Fig. 3, A).

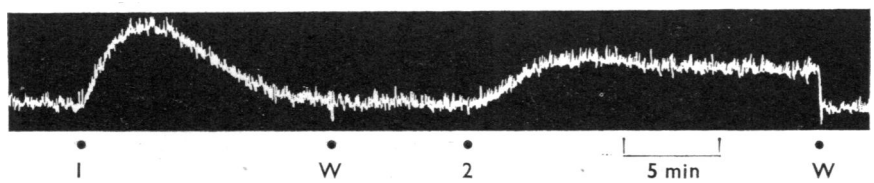


Fig. 2. Responses of a spiral strip of the terminal bile duct from a calf. At 1, adrenaline (1 $\mu$g/ml.). At 2, phenylephrine (1 $\mu$g/ml.). In this, and in later figures, the time mark indicates an interval of 5 min, and W indicates that the bath fluid was removed and replaced with fresh.

Fig. 3 illustrates the effect of adrenaline in contracting a spiral strip of terminal bile duct and in relaxing the longitudinal muscle of a segment of duodenum which surrounded the terminal bile duct. The potency of the drugs on the longitudinal muscle of the duodenum obtained from the vicinity of the terminal bile duct was in the order: isoprenaline, noradrenaline, adrenaline and phenylephrine.

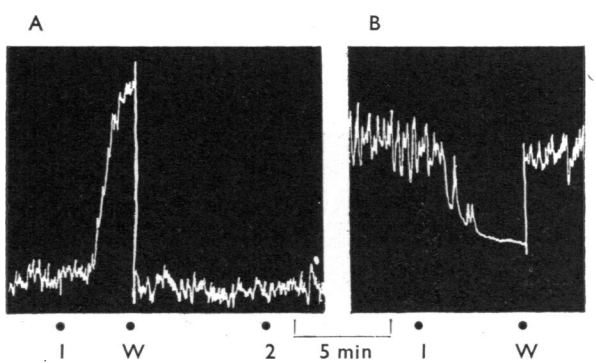


Fig. 3. A: responses of a spiral strip of the terminal bile duct from a calf. B: responses of a longitudinal strip of duodenum taken from the vicinity of the terminal bile duct of a calf. At 1, adrenaline (0.5 $\mu$g/ml.). At 2, isoprenaline (0.5 $\mu$g/ml.).

Dibenamine hydrochloride (0.5 to 10 $\mu$g/ml.) antagonized the action of adrenaline in contracting the bile duct, but not in relaxing the duodenum (Fig. 4).

Dichloroisoprenaline reduced the relaxation of the duodenum caused by adrenaline, but only in concentrations higher than 10 $\mu$g/ml.: these concentrations also reduced the effect of adrenaline in contracting the bile duct.

*Intact bile duct*

Figs. 5 and 6 show representative responses of the preparations, isolated from the cat and calf respectively, showing the rhythmic spontaneous longitudinal contractions of the segment of bile duct and the flow of Tyrode solution through the bile duct. The flow through the duct was associated with periodic relaxation of the circular muscle ; the pressures required to force fluid through the lumen were 5 to

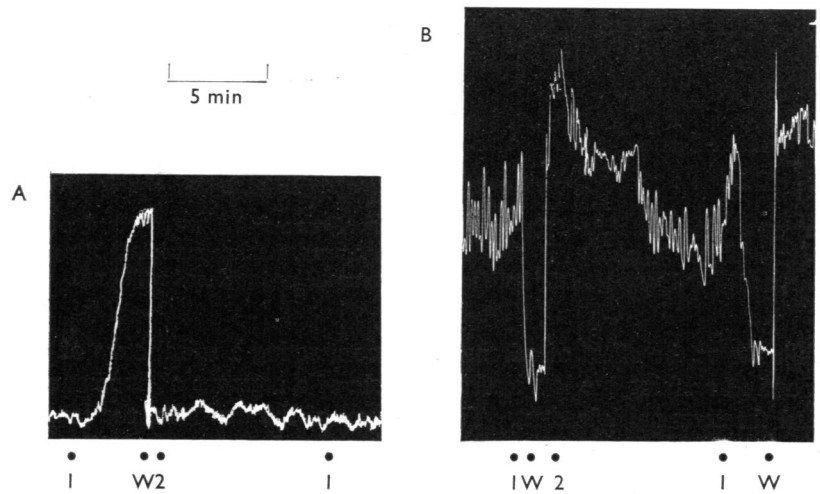


Fig. 4. A: responses of a spiral strip of terminal bile duct from a calf. B: responses of a longitudinal strip of duodenum from the region surrounding the bile duct of a calf. At 1, adrenaline (1 $\mu$g/ml.). At 2, dibenamine (3 $\mu$g/ml.) left in contact for 25 min.

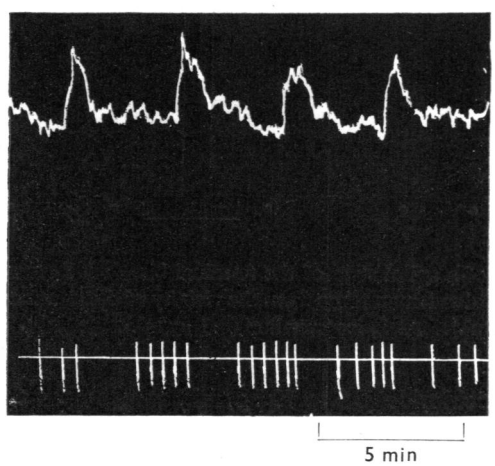


Fig. 5. Responses of a terminal bile duct of a cat. Upper record: longitudinal movements. Lower record: flow (each vertical line indicates a single drop). Note that the flow ceases during contractions of the longitudinal muscle.

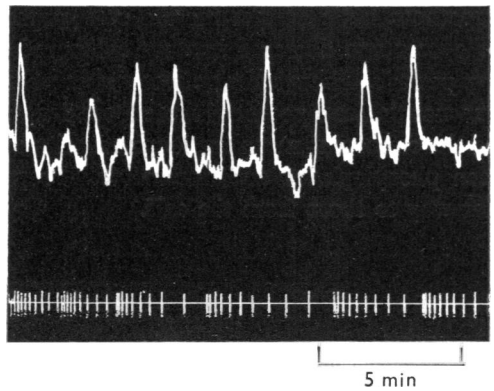


Fig. 6. Responses of a terminal bile duct from a calf. Upper record: longitudinal movements. Lower record: flow (in drops of fluid). Note that the periodic variations in flow are not synchronous with the longitudinal movements.

7 cm of water in preparations from the calf, and more than 10 cm of water in preparations from the cat.

In preparations from both the cat and the calf, adrenaline, noradrenaline and phenylephrine contracted the longitudinal and circular smooth muscle. Starting with a very low concentration of adrenaline and gradually increasing it, the first demonstrable effect was a reduction of the flow through the bile duct; this reduction sometimes appeared with a concentration as low as 0.2 ng/ml. (Crema, Benzi & Berté, 1962). In Fig. 7 the relationship is plotted between reduction in flow and

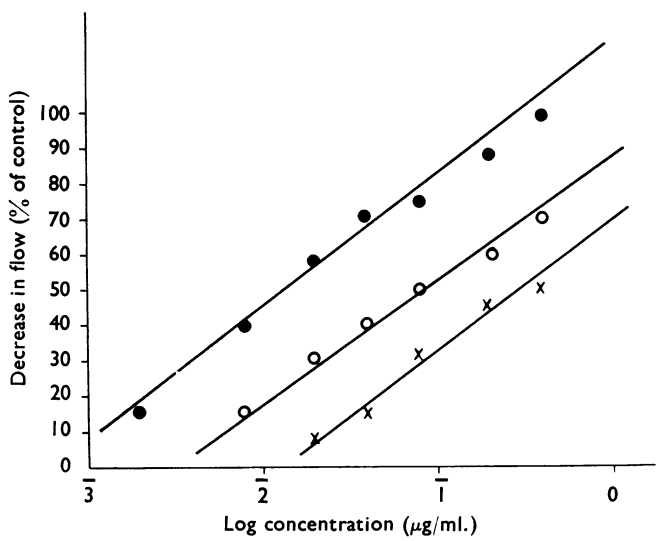


Fig. 7. Calf's terminal bile duct. Concentration/response curves for phenylephrine (●), adrenaline (○) and noradrenaline (×). The ordinate represents the decrease of flow (% of control) produced by the drugs.

the doses of the sympathomimetic amines for the calf preparation: the responses are expressed as the percentage decrease in flow compared with the flow in the immediately preceding period. Phenylephrine was the most potent, adrenaline was next and noradrenaline was the least potent of these three drugs. Thus phenylephrine has a greater effect on the circular than on the longitudinal muscle ; Fig. 8 illustrates this difference between phenylephrine and adrenaline. Preparations from the cat responded in a similar way to those from the calf.

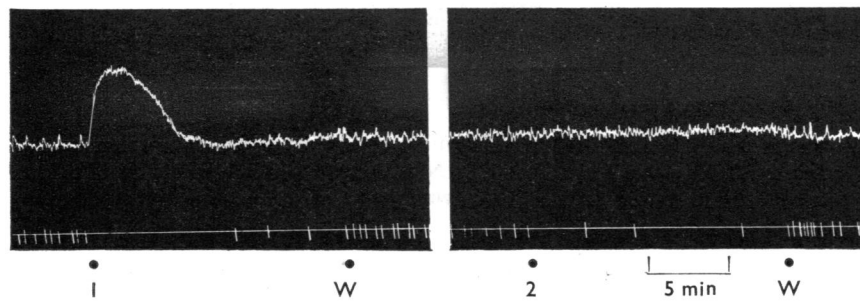


Fig. 8. Responses of the terminal bile duct of a calf. Upper record: longitudinal movements. Lower record: flow (in drops). At 1, adrenaline (0.4 μg/ml.). At 2, phenylephrine (0.04 μg/ml.).

In some experiments with preparations from the calf, adrenaline and noradrenaline had biphasic actions on flow, an initial decrease in flow being followed by an increase. Similar observations have been made with acetylcholine and histamine.

The usual actions of adrenaline could still be observed when the preparation has had its muscle tone increased by barium chloride (Fig. 9) or by carbachol. Similarly, after the tone of the preparation had been decreased by other drugs, the effect of adrenaline remained. For example, when the flow through the bile duct is increased by papaverine, it can then be reduced again by adrenaline. Fig. 10 shows that cholecystokinin (Cecekin, Vitrum) greatly increased the flow through the duct but

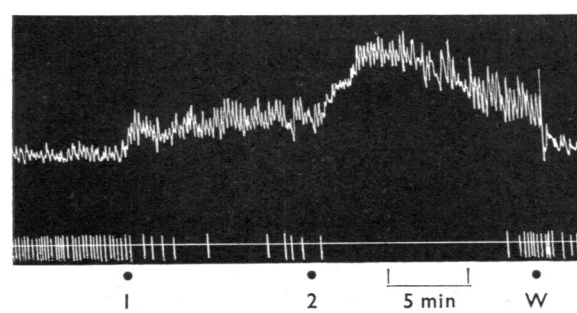


Fig. 9. Responses of the terminal bile duct of a calf. Upper record : longitudinal movements. Lower record : flow (in drops). At 1, barium chloride (20 μg/ml.). At 2, adrenaline (0.6 μg/ml.).

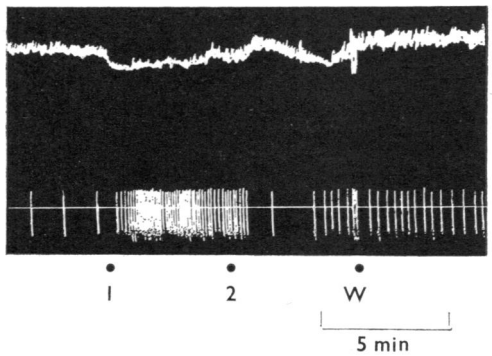


Fig. 10. Responses of the terminal bile duct of a cat. Upper record: longitudinal movements. Lower record: flow (in drops). The flow was strongly increased by cholecystokinin (5 $\mu$g/ml.) at 1, and then decreased by adrenaline (0.4 $\mu$g/ml.) at 2. Note the relaxation of the longitudinal musculature due to cholecystokinin.

that the flow was reduced by adrenaline added in the presence of the cholecystokinin; similar results have been obtained in preparations in which the flow was increased by atropine.

The effects of isoprenaline were somewhat irregular. In preparations from the calf there was usually no effect on spontaneous activity with concentrations from 0.01 to 3.0 $\mu$g/ml., although in some experiments there was a small increase in the flow. However, if the tone of the smooth muscle was increased by carbachol (0.005 to 0.05 $\mu$g/ml.) then isoprenaline regularly caused a relaxation, indicated by an increase in flow. Higher concentrations of isoprenaline (more than 5 $\mu$g/ml.) reduced flow: this result may be analogous to that obtained with high concentrations of isoprenaline by Thompson (1958) with the isolated nictitating membrane and by Luduena (1962) with the rabbit perfused ear.

In preparations of bile duct from the cat, isoprenaline always increased flow (Fig. 11). The sensitivity of the cat bile duct to isoprenaline decreased rapidly during the first hour of an experiment; it was therefore impractical to determine valid dose/response curves.

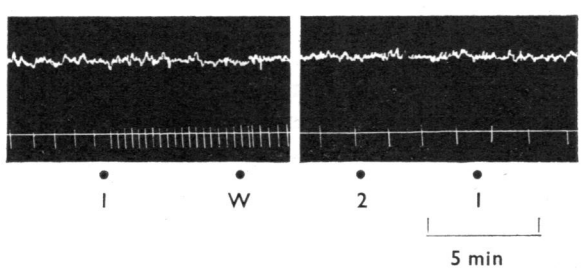


Fig. 11. Responses of the terminal bile duct of a cat. Upper record: longitudinal movements. Lower record: flow (in drops). At 1, isoprenaline (0.2 $\mu$g/ml.). At 2, dichloroisoprenaline (5 $\mu$g/ml.).

Dichloroisoprenaline (5 to 10 μg/ml.) blocked the action of isoprenaline in increasing flow through the duct (Fig. 11). Higher concentrations of dichloroisoprenaline (over 10 μg/ml.) were required to block the decrease in flow caused by adrenaline; these concentrations also reduced the responses to histamine and acetylcholine. Dichloroisoprenaline (10 to 30 μg/ml.) affected the bile duct directly, increasing the tone and the rhythmicity and decreasing the flow.

Dibenamine (0.1 to 1.0 μg/ml.) completely blocked the effects of adrenaline, noradrenaline and phenylephrine on terminal bile duct preparations from both cat and calf.

In some experiments the action of adrenaline (1 to 5 μg/ml.) was reversed by dibenamine (5 to 30 μg/ml., applied for 20 min) or by phentolamine (40 to 80 μg/ml.). This phenomenon was observed only with occasional preparations of bile duct from the calf but was frequently observed with preparations from the cat.

## DISCUSSION

The smooth muscle of the terminal portion of the bile duct, taken from the cat or the calf and freed from the adjacent duodenal smooth muscle, contracts in response both to sympathomimetic and to parasympathomimetic drugs. In previous work we obtained similar results with bile duct from the dog and the pig (Crema & Benzi, 1961). Acetylcholine and adrenaline also lack opposing actions on smooth muscle from other sites, for example the nictitating membrane, the vas deferens and the seminal vesicles.

Noradrenaline is less potent than adrenaline in contracting the smooth muscle of the bile duct; this finding holds both for spiral strips of bile duct and for the isolated intact duct. Thompson (1958) reported that adrenaline was more potent than noradrenaline in contracting the cat's isolated nictitating membrane. Phenylephrine, which according to Levy & Ahlquist (1961) activates only α-receptors, acts in a qualitatively similar manner to adrenaline; it appears less potent if the maximum height of the responses is measured but more potent if the duration of the responses is used. Isoprenaline, which can be considered to act on β-receptors, regularly dilates the bile duct from the cat, and is inactive or occasionally dilates the calf's bile duct. The results with the anti-adrenaline drugs dibenamine and dichloroisoprenaline, which block α- and β-receptors respectively, suggest that receptors of both types are present in the smooth muscle of the bile duct, occupation of the former leading to contraction and of the latter to relaxation. This situation is also found in the smooth muscle of the bronchioles (Castro de la Mata, Penna & Aviado, 1962). The duodenal smooth muscle adjacent to the end of the bile duct is relaxed by the sympathomimetic drugs which contract the bile duct.

With the preparation of the terminal segment of bile duct it is difficult to distinguish between its musculature and that of the duodenum and it is perhaps unavoidable that the sphincter of the duct contains some duodenal muscle fibres. It is possible, therefore, that the β-receptors which we deduce to be present in our preparations of bile duct could be associated with some duodenal tissue remaining attached to the bile duct. However, it would then be even more difficult to explain the action of adrenaline in contracting the bile duct. Although adrenaline can

contract some parts of the gastro-intestinal tract in certain species (Brunaud & Labouche, 1947; Munro, 1951), and certain muscle layers of the intestine (King & Robinson, 1945), we have never observed contraction of parts of duodenum taken from the vicinity of the termination of the bile duct.

The responses of some smooth muscle preparations to adrenaline can be altered by a change in their tone (Hermansen, 1961). It was for this reason that experiments were carried out with the bile duct in which the tone was increased or decreased by various drugs; however, the usual contractile response to adrenaline persisted.

The results reported here seem to suggest that the bile duct can be functionally independent of the duodenum. However, in our more recent experiments (unpublished) with the bile duct *in situ* we have demonstrated that the duodenum is dominant over the autonomy of the bile duct.

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