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ACTIONS OF SYMPATHOMIMETIC DRUGS ON THE SMOOTH MUSCLE AT THE JUNCTION OF THE BILE DUCT AND DUODENUM STUDIED IN SITU

BY

G. BENZI, F. BERTÈ, A. CREMA AND G. M. FRIGO

From the Department of Pharmacology, University of Pavia, Italy

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The actions of adrenaline, noradrenaline, phenylephrine and isoprenaline have been examined on flow through the terminal bile duct and on the tone of the duodenum in the vicinity of the terminal bile duct. These drugs were injected intravenously, or intra-arterially into the blood supply of the junction of the bile duct and duodenum. The effects of the antagonistic drugs, dibenamine and dichloroisoprenaline, were also tested. Isoprenaline always relaxed the duodenum and increased the flow through the bile duct. Adrenaline, noradrenaline and phenylephrine relaxed the duodenum, but had variable effects on the flow through the bile duct. It is concluded that adrenaline acts directly on the smooth muscle of the bile duct to contract it, but the influence of the neighbouring duodenal muscle may nevertheless result in an increase in flow through the duct.

There have been contradictory reports about the action of sympathomimetic drugs on the smooth muscle at the junction of the bile duct and the duodenum (Oddi's sphincter). According to some authors these drugs induce a relaxation (Winkelstein & Aschner, 1924; Burget, 1925; Iwanga, 1925; Lueth, 1931; Shi, 1933; Bergh, 1942; Lorenzini & Elzenbaum, 1952; Ishioka, 1959; Pasechnik, 1959; Stalport, Nicolas, Demelenne & Horeczki, 1959; Stille & Hilfiker, 1962), but others have reported differently (Reach, 1920; McWhorther, 1921; Lueth, 1931; Doubilet & Colp, 1937; Poilleux, Goidin & Nicolaidis, 1952; Erdmann & Henne, 1953; Taccani & Zaffagnini, 1953a, b; Fogliati, Ciocatto, Cattaneo & Giudice, 1954; Granser, Hertting, Rissel & Wewalka, 1956; Menguy, Hallenbeck, Bollman & Grindlay, 1958; Pasechnik, 1959).

In previous studies from this laboratory it was found that both sympathomimetic and parasympathomimetic drugs contracted Oddi's sphincter isolated as a strip from the dog, cat, pig and calf (Crema & Benzi, 1961). The terminal bile duct responded to drugs in the same way whether: (1) the strips prepared from it were cut spirally, longitudinally or transversally; (2) the tract had or had not been embedded in the duodenal wall; and (3) the degree of muscular tone preceding the application of drugs was high or low. On the terminal bile duct isolated *in toto* adrenaline, noradrenaline and phenylephrine produced a contraction, but isoprenaline produced a relaxation (Crema & Bertè, 1963). In other experiments the tissues comprising the junction of the bile duct and duodenum have been isolated

with their blood vessels intact; drugs were injected into the artery supplying the junction. When the duodenum was in an isotonic condition, adrenaline induced an increase in the flow through the common bile duct in 85% of the experiments. But if the duodenum was mounted in such a way as to limit the spontaneous movements of the longitudinal fibres, adrenaline decreased the flow through the common bile duct in 70% of the experiments. It appeared from these observations that the changes in duodenal muscles were influencing the flow through the bile duct (Crema, Bertè, Benzi & Frigo, 1963).

This paper reports the effects of some sympathomimetic drugs which have now been tested on the junction of the bile duct and duodenum *in situ*.

METHODS

The results reported here were obtained in experiments on seventy-seven cats and forty-six dogs.

The animals were anaesthetized at first with ether, followed by chloralose (intravenously 80 mg/kg for the cat and 100 mg/kg for the dog). Further injections of chloralose were given when necessary during the experiment. Most animals (including all those for which Figures have been chosen) were previously treated with atropine sulphate (1 mg/kg, subcutaneously). All animals were given artificial ventilation. Arterial blood pressure was measured from a cannula inserted into a carotid or femoral artery.

After laparotomy, a cannula was inserted into the bile duct pointing towards the duodenum, and a draining tube was inserted into the central end of the duct. The flow through the terminal bile duct was regulated by adjusting the height of a Mariotte bottle containing Tyrode solution, and the flow was measured by a drop-counter inserted between the bottle and the duct. The pressure necessary to produce a regular flow through the terminal bile duct of 3 to 6 drops/min (25 drops was equal to 1 ml.) ranged from 12 to 25 cm of water; this agrees with observations made by others (Granser *et al.*, 1956; Sterling, 1955).

Movements of the duodenum were recorded by inserting a water-filled rubber balloon approximately 3 to 6 cm below the opening of the bile duct, so that it would not affect the activity of the sphincter. Because we were particularly interested in studying the behaviour of the duodenal musculature in the immediate neighbourhood of the terminal bile duct we

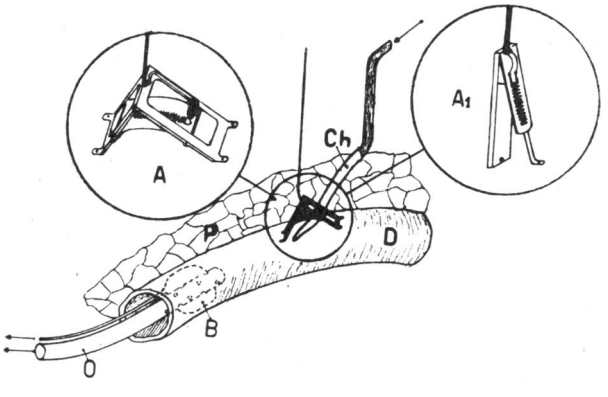

Fig. 1. Strain gauge for recording the movements of the duodenum near the insertion of the bile duct. A, Strain-gauge of the type used by Mallos (1962); A_1, modified strain gauge used in some experiments; Ch, bile duct; P, pancreas; D, duodenum; B, balloon for recording duodenal movements; and O, outflow tube for draining duodenum.

applied strain gauges in that region. Two kinds of strain gauge were used: one similar to that employed by Mallos (1962), and another modified in shape and size to fit the cat's duodenum better. The strain gauge was mounted on the duodenum wall so that it spanned the intramural part of the bile duct (Fig. 1).

In all the experiments on dogs, drugs were injected intravenously. In experiments on cats injections were given intravenously and sometimes intra-arterially as well. These experiments were performed in the cat only because, for technical reasons, it was more suitable than the dog. In order to inject drugs into the arteries supplying the bile duct-duodenum junction (Reighard & Jennings, 1961) the hepatic artery was cannulated beyond the origin of the gastroduodenal artery, in the opposite direction to the blood flow. Except for the gastroduodenal and the superior pancreaticoduodenal arteries, all the other branches of the hepatic and of the gastroduodenal arteries were ligated. At the conclusion of each experiment, a dye was injected into the artery in order to check its distribution. In most experiments the dye was distributed to a small area of the duodenum and pancreas, including the sphincter region; the first part to be coloured, and the part which stained the most, was the terminal bile duct. By this method the local blood circulation was kept normal, except for the 0.3 ml./min of Tyrode solution (with or without drugs) infused by a pump through the cannula inserted into the hepatic artery.

Other experiments were carried out to study the action of drugs simultaneously on the organ *in situ* and isolated, but under as nearly as possible the same conditions; we employed a method similar to that described by Vane (1958) for maintaining isolated tissue in exteriorized circulating blood. Heparinized blood was led from a carotid artery of a cat through two siliconed organ-baths. The total quantity of blood in the external circuit was 40 ml. The first bath contained the terminal part of a bile duct taken from another cat: the flow through it and the movements of the longitudinal musculature were recorded (Crema, Benzi & Bertè, 1962). The second bath contained a piece of duodenum about 2 cm long taken just caudal to the biliary opening; its longitudinal movements were recorded. The blood from the baths was returned by a pump to a femoral vein of the cat, into which 40 ml. of cat blood were also infused. In the cat supplying blood to these organ-baths measurements were made of the flow through the terminal part of the bile duct, duodenal movements and blood pressure.

The following drugs were used, amounts of each are expressed in terms of the bases: (−)-adrenaline hydrochloride, (−)-noradrenaline bitartrate, (−)-phenylephrine hydrochloride, (±)-isoprenaline hydrochloride, (±)-dichloroisoprenaline hydrochloride and dibenamine hydrochloride.

RESULTS

Responses to intravenous injections of drugs

The effects of intravenous injection of adrenaline (1 to 5 μg/kg), noradrenaline (1 to 5 μg/kg), phenylephrine (10 to 30 μg/kg) and isoprenaline (0.5 to 5 μg/kg) on the flow through the bile duct of cats and dogs are summarized in Tables 1 and 2. The response was taken as the flow during the 3.5 min period immediately after

TABLE 1

EFFECTS IN CATS OF SOME SYMPATHOMIMETIC DRUGS, INJECTED INTRAVENOUSLY, ON FLOW THROUGH THE BILE DUCT

The figures are the percentages of cats responding in each way (total of fifty cats)

Change in flow through bile duct	Cats (%) responding to			
	Adrenaline	Noradrenaline	Phenylephrine	Isoprenaline
Increase	62	60	60	100
Decrease	32	36	30	0
No change	6	4	10	0

TABLE 2

EFFECTS IN DOGS OF SOME SYMPATHOMIMETIC DRUGS, INJECTED INTRAVENOUSLY, ON FLOW THROUGH THE BILE DUCT

The figures are the percentages of dogs responding in each way (total of forty dogs)

Change in flow through bile duct	Dogs (%) responding to			
	Adrenaline	Noradrenaline	Phenylephrine	Isoprenaline
Increase	90	90	90	100
Decrease	7·5	5	5	0
No change	2·5	5	5	0

injection and this was compared with the flow during the 3.5 min immediately before the injection. Each animal was given adrenaline, noradrenaline, phenylephrine and isoprenaline; initially at the lowest of the stated doses, namely 1, 1, 10 and 0.5 μg/kg; then 3, 3, 20 and 2.5 μg/kg; and finally 5, 5, 30 and 5 μg/kg respectively. The type of response to each drug was generally consistent for all tested doses, except with a limited number of animals (four cats and two dogs). In this latter group of animals the change in type of response during the course of experiments was not a result of the variation in dosage, since the same dose produced different responses; these results do not appear in Tables 1 and 2. In the majority of the animals (forty-five cats and thirty-eight dogs) the response to the drugs was evident at the lowest doses, but in five cats and two dogs the response was seen only with the higher doses; these results are also included in Tables 1 and 2. In some animals, the lack of response to all the tested doses, reported in the Tables 1 and 2 as "no change," is attributed to the insensitivity of the animal or to a biphasic response, as the total flow remained unchanged during the 3.5 min after injection.

Adrenaline produced an increase in flow in the bile duct in 62% of the cats and in 90% of the dogs. In a few of these experiments the increase occurred after a short latent period or after a momentary decrease in flow. Generally, the increase in flow through the bile duct and the relaxation of the duodenum occurred simultaneously. In the dog, an increase of the flow was also observed when the duodenum was hypotonic. The return of duodenal motility to its previous condition was not always synchronized with the return of flow through the bile duct to its previous value: the action on the bile duct usually lasted longer than on the duodenum.

Phenylephrine increased the flow in 60% of the cats and in 90% of the dogs, as did adrenaline (Tables 1 and 2). The records from an experiment in a dog given 15 μg/kg of phenylephrine are shown in Fig. 2. In the cat, even high doses of phenylephrine (40 to 50 μg/kg) did not produce an increase in flow as large as that induced by adrenaline, although the responses to these two drugs were qualitatively the same. Noradrenaline gave responses similar to those of adrenaline in both the cat and the dog (Tables 1 and 2). In the dog, the responses to drugs remained consistent throughout most experiments, and lent themselves to the construction of dose/response curves testing further doses (Fig. 3).

In about one-third of the cats adrenaline, phenylephrine and noradrenaline reduced the flow through the bile duct; this we interpret as constriction of the duct.

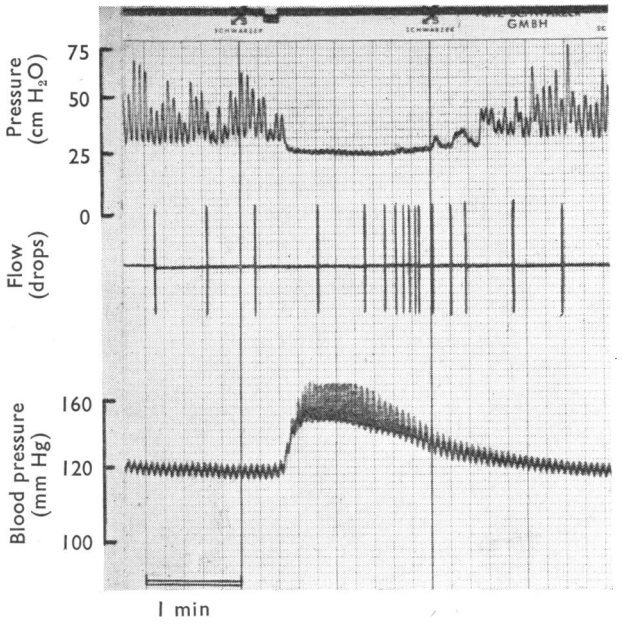

Fig. 2. Effect of phenylephrine (15 μg/kg, intravenously) in a dog weighing 12·6 kg. Injection at mark on top trace. The records, from top to bottom : pressure in balloon in duodenum, flow through terminal bile duct in drops and blood pressure. Horizontal time calibration, 1 min.

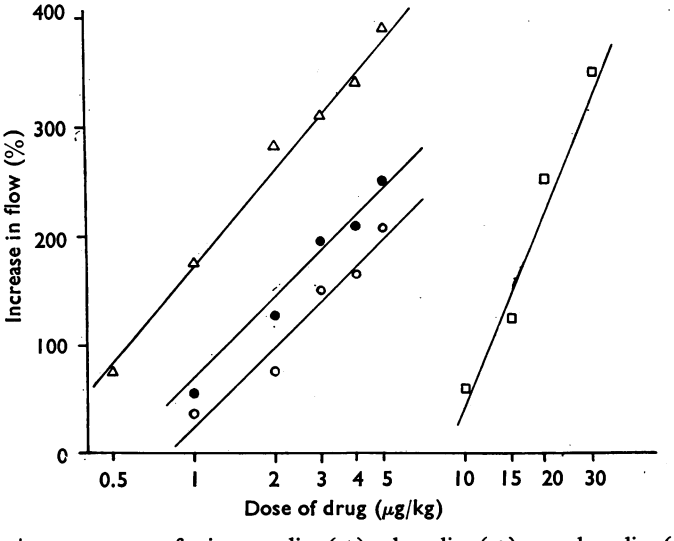

Fig. 3. Log dose/response curves for isoprenaline (△), adrenaline (●), noradrenaline (○) and phenylephrine (□) in the dog. The doses of drugs (μg/kg, intravenously) are plotted on the abscissae : note logarithmic scale. The ordinate shows the increase in flow through the bile duct as a percentage of the control flow $\left(\frac{\text{new flow—old flow}}{\text{old flow}} \times 100\right)$.

The reduction in flow, when it occurred, was unrelated to the presence or absence of atropine, or whether or not the vagus nerves were divided. In these experiments we made the following observations:

(1) In four cats, constriction of the duct appeared to be related to the change in blood pressure since a similar response was obtained by injecting intravenously 10 ml./kg of a 5% solution of glucose (Fig. 4) or 10 ml./kg of Tyrode solution. The importance of the vascular component has been emphasized also by Arianoff (1959).

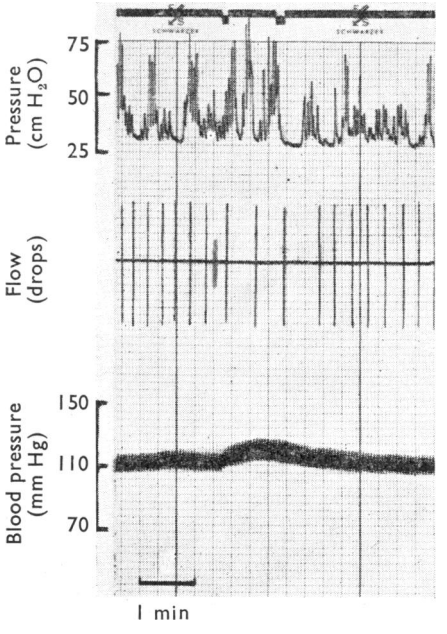

Fig. 4. Records as in Fig. 2 obtained from a cat, 2·6 kg. The experiment shows that the intravenous infusion of 10 ml./kg of a 5% solution of glucose decreased the rate of flow through the bile duct and slightly increased the blood pressure. The infusion was given between the two marks in the upper trace.

(2) In four cats, the decrease in flow appeared to be related to the state of tone and the activity of the duodenum. In these experiments adrenaline produced a dilatation after the injection of carbachol or morphine had led to an increase in tone and motility of the duodenum (Fig. 5).

(3) In eight experiments the action of adrenaline was not related to a change in blood-pressure or to the tone of the intestine.

Dichloroisoprenaline (6 mg/kg) injected intravenously increased the rate of flow through the bile duct and relaxed the duodenum (Fig. 6,*c*). This effect was observed in both cat and dog. After dichloroisoprenaline the increase in the flow induced by adrenaline was still present (Fig. 6,*d*). Adrenaline also induced a further decrease in the tone of the duodenum. However, dichloroisoprenaline prevented the action of isoprenaline (Fig. 7). In animals previously injected with 2 to 5 mg/kg of dichloro-

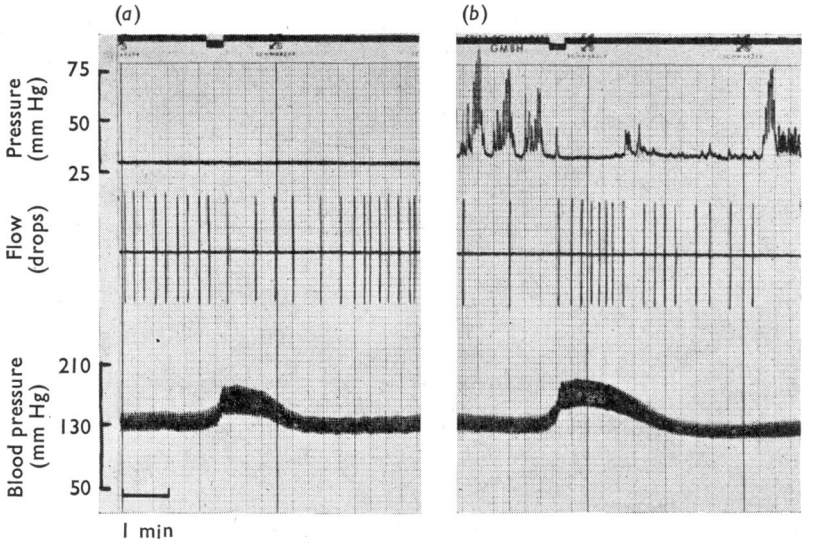

Fig. 5. Records as in Fig. 2, obtained from a cat, 2·3 kg. (*a*) the intravenous injection of 2 μg/kg of adrenaline decreased the flow through the bile duct ; at this time the duodenum was atonic Between (*a*) and (*b*), 10 μg/kg of morphine was injected intravenously. (*b*) When the duodenum had attained rhythmic movements and tone, the injection of adrenaline (3 μg/kg) now increased the flow through the duct and relaxed the duodenum.

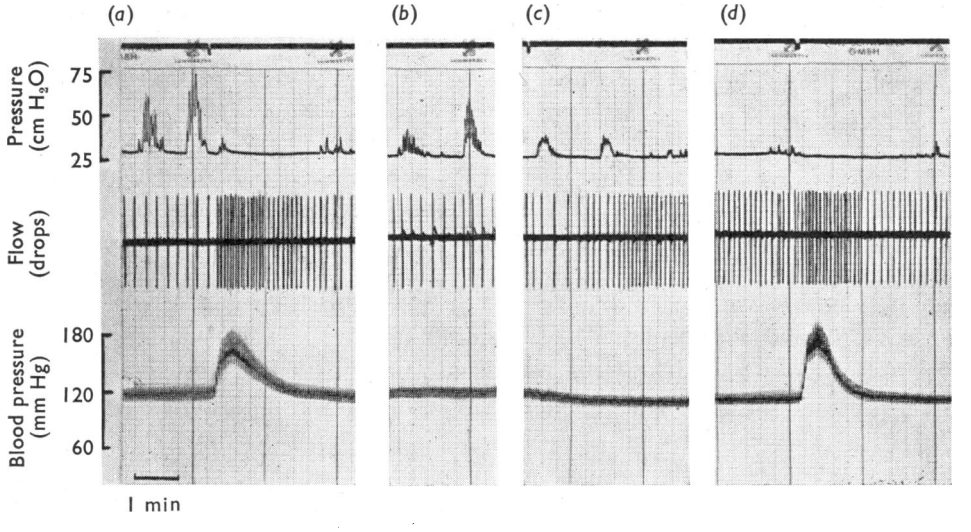

Fig. 6. Effects of adrenaline and dichloroisoprenaline in a dog of 16 kg. The records are as in Fig. 2. (*a*), intravenous injection of 2·5 μg/kg of adrenaline increased flow through the bile duct and relaxed the duodenum. (*b*), taken 10 min later shows return to the previous conditions. Dichloroisoprenaline (6 mg/kg) was injected intravenously in (*c*). It failed to block the response to a subsequent injection of adrenaline (2·5 μg/kg), in (*d*).

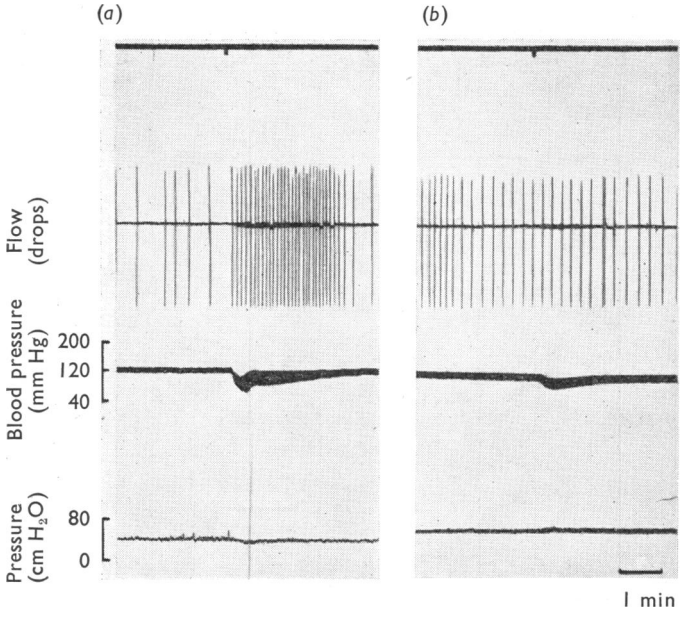

Fig. 7. Block of response to isoprenaline by dichloroisoprenaline. The experiment was on a cat of 2·5 kg. The records from above down are : flow through the terminal bile duct, the vertical lines indicate drops ; blood pressure ; and pressure in a balloon in the duodenum. Isoprenaline (4 μg/kg) was injected at the marks in (*a*) and (*b*). Between the panels, 3 mg/kg of dichloroisoprenaline was injected intravenously.

isoprenaline and 5 to 20 mg/kg of dibenamine (given 30 min before), the actions of adrenaline were blocked.

Intra-arterial injections of drugs

The results of experiments in which drugs were infused into the blood vessels supplying the region of the bile duct-duodenal junction are shown in Table 3. This Table contains only the results from those sixteen experiments in which a later injection of dye showed localization of the region perfused. The following quantities were infused during a 3 min period: adrenaline 1, 2 and 4 μg, isoprenaline 1, 2 and 4 μg and phenylephrine 10, 20 and 40 μg.

In these experiments isoprenaline regularly caused an increase in flow through the bile duct, as it did on intravenous injection. However, adrenaline and phenyl-

TABLE 3

EFFECTS IN CATS OF SOME SYMPATHOMIMETIC DRUGS INFUSED INTO THE BLOOD VESSELS SUPPLYING THE DUODENAL-BILE DUCT JUNCTION IN SITU

Change in flow in bile duct	Number of cats (out of 16) responding to		
	Adrenaline	Phenylephrine	Isoprenaline
Increase	4	3	16
Decrease	11	11	0
No change	1	2	0

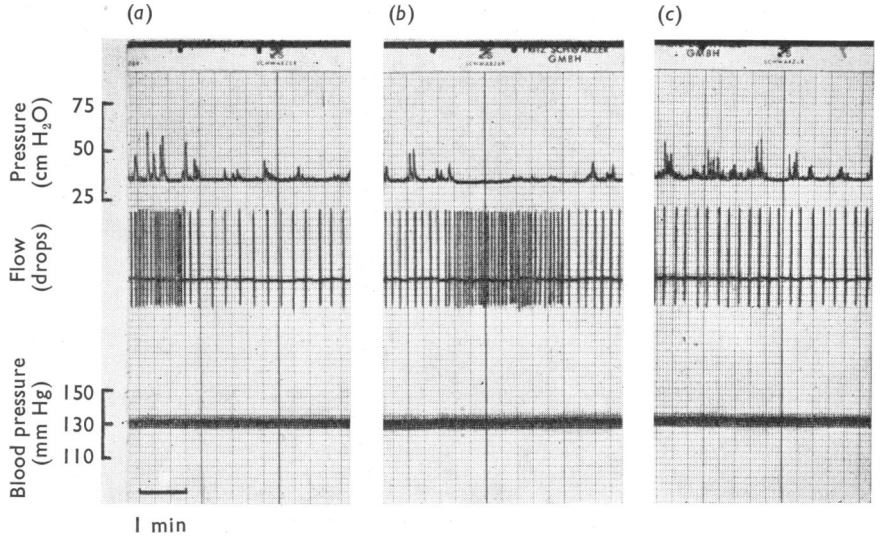

Fig. 8. Responses to adrenaline given by intra-arterial infusion and the effects of dibenamine and dichloroisoprenaline. The records are as in Fig. 2. The experiment is from a cat of 3·2 kg. Intra-arterial infusions of adrenaline (4μg) into the artery were given between the marks on the upper trace in each panel. Dibenamine (20 mg/kg) was injected intravenously between (*a*) and (*b*). Dichloroisoprenaline (5 mg/kg) was injected intravenously between (*b*) and (*c*).

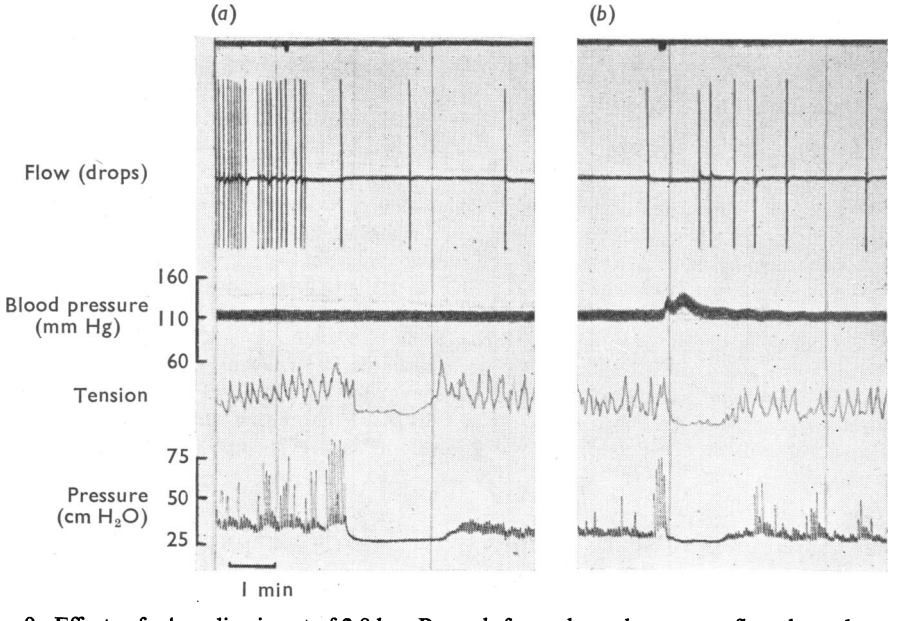

Fig. 9. Effects of adrenaline in cat of 2·8 kg. Records from above down are : flow through terminal bile duct, vertical lines indicate drops ; blood pressure ; tension across strain gauge (magnification twelve times) spanning the wall of the duodenum over the terminal bile duct ; and pressure in a balloon inserted in the duodenum. (*a*), adrenaline (4 μg) was infused into the pancreaticoduodenal artery between the marks. (*b*), adrenaline (2 μg/kg) was injected intravenously at the mark.

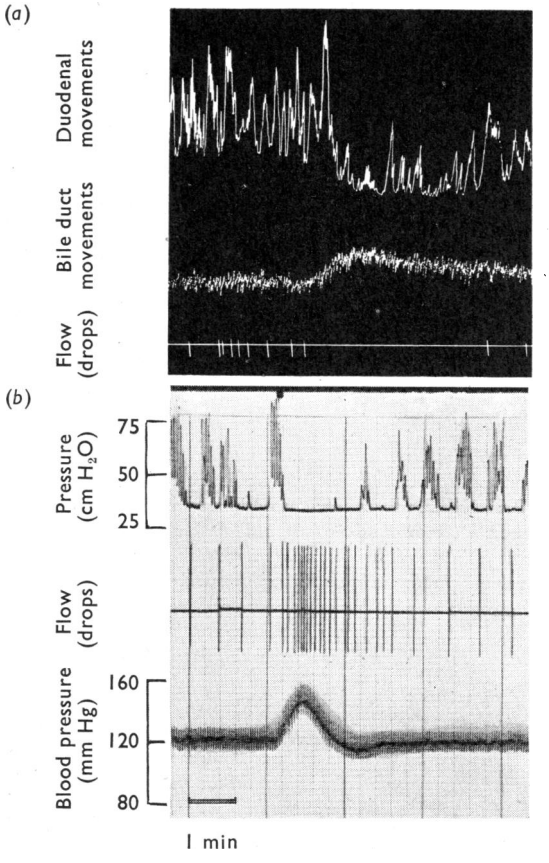

Fig. 10. Effects of adrenaline on bile duct and duodenum, *in situ* and isolated. The kymograph records in (*a*) are : longitudinal movements of segment of duodenum taken from a cat, suspended in an organ-bath and bathed with blood recirculated from the cat providing the observations shown in (*b*) ; longitudinal movements of bile duct ; and flow through the bile duct isolated from a cat suspended in another blood-bathed organ-bath. The records in (*b*) are from a 4·2 kg cat donating the blood circulating through the baths containing the organs in (*a*). From above downward : pressure in balloon inserted in duodenum ; drops flowing through the terminal bile duct ; and blood pressure. Adrenaline (2 μg/kg) was injected intravenously into the cat at the mark shown above the records in (*b*). Note that the isolated bile duct was constricted and the bile duct *in situ* was dilated. However, the duodena were relaxed both *in situ* and isolated.

ephrine caused an increase in flow in only 25% and 19% respectively of the experiments compared with 62% and 60% when these drugs were injected intravenously. In some experiments adrenaline and phenylephrine had a biphasic action consisting of an initial decrease followed by an increase in flow. When adrenaline injected into the pancreaticoduodenal artery decreased the flow, treatment with dibenamine (20 mg/kg, intravenously) resulted in a reversal of the response. Then subsequent treatment with dichloroisoprenaline (5 mg/kg, intravenously) completely abolished the response to adrenaline (Fig. 8).

Records of the tone and of the motility of the duodenum just surrounding the entrance of the biliary tract obtained by means of a strain gauge have shown that constriction of the terminal duct caused by adrenaline was synchronous with relaxation of the duodenum (Fig. 9).

Comparison of responses of bile duct and duodenum, isolated and in situ

Fig. 10 shows the results from one of five experiments in which adrenaline (2 μg/kg) was injected intravenously into a cat; it increased the flow through the bile duct and relaxed the duodenum. However, the isolated bile duct (taken from another cat, but contained in an organ-bath and bathed by the blood) responded with a decrease in flow, although the isolated duodenum relaxed.

DISCUSSION

The lack of uniformity in the response of the biliary tract to sympathomimetic drugs has been observed by many authors. In our experiments the intravenous injection of adrenaline, noradrenaline and phenylephrine usually caused a dilatation of the terminal bile duct, and isoprenaline caused a dilatation. However, according to Granser *et al.* (1956) isoprenaline is ineffective in relaxing the bile duct which has been contracted by spasmogenic drugs. When the sympathomimetic drugs were injected into the superior pancreaticoduodenal artery, adrenaline and phenylephrine usually caused a constriction of the duct while isoprenaline still caused dilatation.

The reason for injecting drugs into the arterial supply to the terminal bile duct was to affect this structure selectively. However, owing to the close anatomical relation between the terminal bile duct and the duodenum, an injected drug would reach the surrounding duodenum even though it reached the terminal bile duct first. An alternative way of affecting the terminal duct selectively would be to introduce drugs into the lumen, but we considered this to be a less desirable procedure from a physiological point of view, and in any case it would not permit a more selective localization of action (Eisenstein, 1949). There is the possibility that drugs injected intra-arterially might exert their effects on the bile duct indirectly by affecting the blood vessels. Whether or not this is true for the bile duct the relaxation of the duodenum as recorded by the strain gauge is produced equally by intra-arterial and by intravenous injection of drugs.

The bile duct when isolated and freed from its neighbouring duodenum responds to adrenaline by constricting (Crema *et al.*, 1962). Isolated spiral strips cut from the terminal bile duct respond to adrenaline by contracting (Crema & Benzi, 1960). However, when the terminal bile duct remains surrounded by the wall of the duodenum into which it is inserted the action of adrenaline seems to depend on the tone and the motility of the duodenum. These observations lead us to conclude that the duodenum interacts with the terminal bile duct in such a way that the latter can show its own response only in some conditions, for instance when isolated or when the duodenum is stretched. However, another possibility is that these different

responses to adrenaline are due to some other differences in the experimental conditions.

If the neighbouring duodenal tissues affect the calibre of the terminal bile duct the difference in response to adrenaline seen in different animal species may be due to the particular anatomical structure of the junction. For instance, the marked increase in flow through the terminal duct produced by adrenaline in the dog could be explained by the long funnel made by the biliary tract inside the duodenal wall in this species: relaxation of the duodenum would have a greater influence in increasing flow than would constriction of the terminal duct in decreasing flow. In favour of the suggestion that the action of adrenaline is to constrict the terminal duct is the constricting action of adrenaline on other portions of the duct, such as Lütkens sphincter (Crema, Bertè, Benzi & Frigo, 1964).

The results obtained with dibenamine and dichloroisoprenaline (α- and β-receptor blocking drugs) were inconclusive. We had previously supposed (Crema & Bertè, 1963) that in the terminal bile duct there were α-receptors, whose occupation by agonists causes a constriction, and β-receptors, whose occupation causes a dilatation. In the duodenum there are also α- and β-receptors, and it was impossible to block the receptors of one organ leaving unaffected those of the other. Moreover, it was impossible to draw a conclusion on the basis of the differential response after the blocking agents, because the two sets of smooth muscle, in the terminal bile duct and in the duodenum, are too unlike in power. For instance, the failure of dichloroisoprenaline to block the action of adrenaline in increasing the flow through the terminal duct could result from the duodenal α-receptors, which when occupied cause a relaxation of the powerful intestinal muscle overcoming the constriction in the bile duct, which occurs when its α-receptors are occupied.

In experiments on the bile duct *in situ* when adrenaline was injected into the pancreaticoduodenal artery, we usually observed a reduction in flow through the terminal bile duct. Sometimes this was followed by a relaxation of the duodenal musculature and an increase in flow. These observations support our contention that adrenaline acts directly on the duct to constrict it, but that changes in the duodenal muscles also influence flow through the duct.

The experiments with the isolated bile duct and duodenum from one cat superfused with the blood of a donor cat have clearly shown that the response of the terminal duct is quite different when the duct is embedded in the duodenum or is freed from it.

We have also attempted to dissociate responses of Oddi's sphincter from responses of the duodenum by studying the effects of stimulation of autonomic nerves (Crema *et al.*, 1964). The unmixed (purely sympathetic or parasympathetic) nerves supplying the junction of the bile duct and the duodenum are few and inconstant, therefore we stimulated the splanchnic nerves or a branch of the vagus above the diaphragm; but in these experiments responses of both the duodenum and the bile duct were always seen. On conclusion, from a strictly pharmacological point of view, the action of the sympathomimetic agents seems to be a relaxation

of the terminal part of the bile duct, but from a physiological point of view a strictly localized liberation of chemical mediators of the sympathetic nerves could induce a constriction of the terminal bile duct.

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