Pharmacological Features of the Gall Bladder and Its Vascular Bed of the Dog *in situ*

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TAMURA, K., ENDOH, M. and HASHIMOTO, K. *Pharmacological Features of the Gall Bladder and Its Vascular Bed of the Dog in situ.* Tohoku J. exp. Med., 1971, 104 (2), 157-169 — Pharmacological features of the gall bladder and its vascular bed were studied by means of the intra-arterial administration of various substances in the dog *in situ*. The contraction of the gall bladder was produced by various compounds as follows: Cholinergic drugs, kinin substances, histamine, ganglion stimulants, ouabain, BaCl₂ and CaCl₂. Meanwhile, adrenergic drugs, ganglion blocking agents, lys-vasopressin, smooth muscle relaxants, KCl and MgCl₂ relaxed the gall bladder. DMPP, 5-HT, nicotine, lobeline, angiotensin and ATP caused a biphasic response, *i.e.*, a contraction followed by a relaxation or a relaxation followed by a contraction. The pharmacological features of cholecystic arteries are not the same as those of the gall bladder: Cholinergic and adrenergic drugs except isoprenaline, and ganglion stimulating and blocking agents produced opposite effects, while smooth muscle stimulants and relaxants acted similarly on both. Among polypeptides, lys-vasopressin relaxed the gall bladder, cholecystikinin constricted it, and gastrin and oxytocin caused no response, while the former constricted the artery and the latter three dilated it. ——— gall bladder; cholecystic artery; polypeptide

Since Bainbridge and Dale (1905) investigated the nervous control of the canine gall bladder, many reports were published on the responses to various substances, including cholinergic and adrenergic compounds, histamine, cholecystikinin, bile salts and morphine (Lieb and McWhorter, 1915; Halpert and Lewis, 1930, Gaensler *et al.* 1948). These studies have been done on whole animals by intravenous administration of compounds or on excised preparations kept in the Tyrode solution. The present authors perfused the canine cholecystic artery with the blood conducted from the femoral artery under a constant perfusion pressure, and drugs were given close-arterially. This enabled the authors to investigate the pharmacological features of the gall bladder.

In a previous paper, Hashimoto and Kumakura (1965) investigated vascular responses to various substances of the mesenteric, renal, coronary and femoral arteries and classified drugs into six groups. Soon later Matsumura *et al.* (1968) studied the pharmacological features of the vasculature of the urinary bladder,

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and Yamamoto *et al.* (1970) studied those of the skin. For extension of such comparative studies, the vascular response of the gall bladder was also investigated in this paper.

METHODS

Twenty-one mongrel dogs of either sex weighing 8 to 15 kg were used. The animals were anesthetized initially by an intravenous injection of 30 mg/kg of sodium pentobarbital, and anesthesia was maintained by infusion of pentobarbital at a rate of 4.5 mg/kg/hr into the jugular vein. The gall bladder was exposed by a wide incision of the abdominal wall along the costal margin in both sides. The cholecystic artery was isolated carefully from the surrounding tissue. A polyethylene cannula, about 1 mm in o.d., was inserted into the distal end of the cut cholecystic artery, through which arterial blood from the femoral artery was perfused. The initial level of blood pressure, 100 to 150 mm Hg, was maintained by transfusion of the fresh blood obtained from other dogs. Sodium ω -heparin (Hashimoto *et al.*, 1963), 500 units per kg was given just prior to the cannulation of the cholecystic artery and additional dose of 1000 units at one-hour intervals. The phrenic nerves were cut bilaterally and costal margin of the diaphragm was removed in order to minimize the effect of the respiratory movements. The trachea was cannulated and a positive pressure respiration was performed by a Harvard respirator (Model 607) at 15 to 20 cpm with a tidal volume of 20 ml per kg of body weight. An electromagnetic flowmeter (Nihon Kohden MF-2a) was used for measuring the blood flow in the cholecystic artery. A polyethylene tube, 3 mm in o.d., was inserted through the common bile duct into the gall bladder and connected with a strain gauge pressure-probe (Toyo Sokki, LPU 0.1) for the measurement of intravesical pressure, which indicates the movement of the gall bladder. The blood flow in the cholecystic artery, the intravesical pressure and the systemic blood pressure at the carotid artery were recorded on an ink-writing oscillograph (Nihon Kohden, WI-205R). The exposed part was covered with a transparent plastic film to keep it moist and warmed with an infra-red lamp between 37° and 39°C. Fig. 1 shows a schematic diagram of the experimental set-up.

Drugs used and their dose ranges are listed in Table 1. Doses of nicotine, *l*-noradrenaline, *l*-adrenaline, lys-vasopressin, gastrin, gastrin-like tetrapeptide (NK-T), oxytocin, elodeisin, adenosine, uridine, DPN and TPN are expressed in terms of the bases. All other drugs were referred to their corresponding salts. One microgram of oxytocin corresponds to 0.46 international units (Boissonas *et al.*, 1961) of oxytocin activity and one microgram of lys-

Fig. 1. Diagram for perfusion of the cholecystic artery, and measurements of cholecystic blood flow and of intravesical pressure of the gall bladder.

TABLE 1. *Dose ranges of investigated drugs*

Compounds	No. of exp.	μg	Drug concentration in blood (g/ml)†
Parasympathomimetics			
Acetylcholine chloride	21	0.01–10	3×10^{-8} to 10^{-5}
Methacholine chloride	3	0.1–10	3×10^{-7} to 10^{-5}
Carbachol chloride	3	0.1–10	
Bethanechol chloride	3	0.1–30	
Choline chloride	3	1–100	3×10^{-6} to 10^{-4}
Pilocarpine hydrochloride	2	1–10	3×10^{-6} to 10^{-5}
Sympathomimetics			
<i>l</i> -Noradrenaline (base)	12	0.01–1	3×10^{-8} to 10^{-6}
<i>l</i> -Adrenaline (base)	12	0.01–1	
<i>l</i> -Isoprenaline hydrochloride	7	0.01–0.1	3×10^{-8} to 10^{-7}
Dopamine hydrochloride	6	10–30	3 to 9×10^{-5}
Tyramine hydrochloride	6	1–100	3×10^{-6} to 10^{-4}
Phenylephrine hydrochloride	6	0.1–10	3×10^{-7} to 10^{-5}
Methoxamine hydrochloride	2	1–10	3×10^{-6} to 10^{-5}
Ephedrine hydrochloride	3	0.1–10	3×10^{-7} to 10^{-5}
Active polypeptides			
Bradykinin (synthetic)	6	0.01–0.1	3×10^{-8} to 10^{-7}
Eledoisin (synthetic)	4	0.01–0.1	
Kallikrein	3	0.01–0.1*	
Angiotensin (synthetic)	6	0.01–1	3×10^{-8} to 10^{-6}
Lys-vasopressin (synthetic)	4	0.01–1	
Oxytocin (synthetic)	4	0.01–1	
Cholecystokinin	6	0.01–0.1*	
Gastrin	2	0.1–2*	3×10^{-6} to 10^{-5}
Gastrin-like tetrapeptide	2	0.1–10*	
Ganglion stimulating agents			
Nicotine	6	1–10	3×10^{-6} to 10^{-5}
Tetramethylammonium chloride	3	10–30	3 to 9×10^{-5}
1,1-Dimethyl-4-phenylpiperazinium iodide (DMPP)	11	1–10	3×10^{-6} to 10^{-5}
Lobeline hydrochloride	2	10–30	3 to 9×10^{-5}
4-(<i>m</i> -chlorophenylcarbamoyloxy)-2-butylnyltrimethylammonium chloride (McN-A-343)	2	10–30	
Ganglion blocking agent			
Tetraethylammonium bromide	2	1†	3×10^{-3}
Other biogenic amines			
5-Hydroxytryptamine creatinine sulfate	6	0.1–10	3×10^{-7} to 10^{-5}
Histamine dihydrochloride	6	0.1–10	
Nucleosides and nucleotides			
Adenosine hydrate	6	10–30	3 to 9×10^{-5}
AMP (disodium salt hydrate)	3	10–30	
ADP (trisodium salt)	3	10–30	
ATP (disodium salt)	5	10–30	
Uridine (base)	3	10–30	
UMP (disodium salt dihydrate)	3	10–30	
UDP (sodium salt trihydrate)	3	10–30	
UTP (trisodium salt dihydrate)	3	10–30	3×10^{-5}
DPN (base)	2	10	
TPN (base)	2	10	
Miscellaneous compounds			
Papaverine hydrochloride	3	10–30	3 to 9×10^{-5}
Theophylline ethylenediamine	3	10–30	
Ouabain (crystal)	2	1–10	3×10^{-6} to 10^{-5}
Procaine hydrochloride	2	1†	3×10^{-3}
KCl	2	1†	
MgCl ₂	2	1†	
CaCl ₂	2	1†	
BaCl ₂	2	1†	
	2	1†	

* In units † In mg. ‡ The value was calculated from mean blood flow.

Fig. 2. Anatomical differences in blood supply to the gall bladder.

Fig. 3 Responses to parasympathomimetics. The intravesical pressure (I.V.P.) of the gall bladder in cm H₂O and the blood flow (B.F.) of the cholecystic artery in ml/min.

vasopressin to 0.27 international units (Fraschini *et al.*, 1964) of pressor activity. *l*-Noradrenaline and *l*-adrenaline dissolved at a concentration of 10 mg/ml in 0.01 N-HCl were diluted with 0.9% saline to make desired concentrations. All other drugs were dissolved in 0.9% saline. The volume of drug solution was 0.01 and 0.03 ml which was administered intra-arterially by Jintan microinjectors in a period of 4 and 10 sec, respectively.

RESULTS

A) Anatomical considerations on the canine gall bladder

The initial intravesical pressure measured between 5 min and 20 min after cannulation of the common bile duct was 12.5 ± 1.2 cm H₂O (mean $\pm$ S.E., $n=17$). Mean and S.E. of the blood flow of the cholecystic artery was 5.1 ± 0.7 ml/min at 120 ± 12.5 mm Hg ($n=13$) of the mean systemic blood pressure. The cholecystic artery ran along the right side of the common bile duct in 9 dogs, along the left side in 10 dogs and both sides in 2 cases as shown in Fig. 2.

Fig. 4. Responses to sympathomimetics. Scales are the same as those in Fig. 3.

B) Responses of the gall bladder and its vascular bed to various substances

1) *Cholinergic compounds* (Fig. 3). Fig. 3 shows one of the typical experiments.

a) *Effect on the contractility of the gall bladder.* Acetylcholine, bethanechol, carbachol, methacholine, choline and pilocarpine produced an increase in the intravesical pressure as shown in upper curves of Fig. 3. Acetylcholine caused a rapid contraction but its duration was short. Effects on the contractility of methacholine, carbachol and bethanechol were long-lasting. Choline acted in a similar manner but a larger dose from 500 to 1,000 times was required in order to obtain similar response. Pilocarpine caused a similar but weaker response than did choline esters.

b) *Effect on the vascular bed.* All of the cholinergic substances mentioned above caused a marked vasodilation. These vascular effects were shorter in duration than their effects on the motility.

2) *Adrenergic compounds* (Fig. 4). Fig. 4 shows one of the typical experiments.

a) *Effect on the contractility of the gall bladder.*

Noradrenaline, adrenaline, isoprenaline, dopamine and tyramine induced a relaxation. A slight contraction was observed following a marked relaxation by use of noradrenaline and adrenaline in a few cases (2 out of 12). Phenylephrine had almost no effect on the gall bladder even when the vasoconstriction occurred obviously. Dopamine and tyramine produced a long-lasting relaxation and their potencies were 1/30 to 1/100 of that of noradrenaline.

b) *Effect on the vascular bed.* All the seven sympathomimetic compounds except isoprenaline produced a vasodilation. Isoprenaline elicited a vasodila-

Fig. 5. Responses to active polypeptides. Scales are the same as those in Fig. 3.

Fig. 6. Responses to ganglion stimulating agents. Scales are the same as those in Fig. 3.

tion. The potencies of dopamine and tyramine were 1/30 to 1/100 of those of adrenaline and noradrenaline but the former two compounds were long-acting.

3) Active polypeptides (Fig. 5).

a) *Effect on the contractility of the gall bladder.* Bradykinin, eledoisin and kallikrein caused an increment of intravesical pressure. Bradykinin and eledoisin were about 50 times more potent than choline esters on the molar base. Angiotens-

Fig. 7. Changes in responses to successive administrations of DMPP. Scales are the same as those in Fig. 3.

in caused an initial relaxation followed by a contraction. Lys-vasopressin produced a simple and long-lasting relaxation in 3 out of 4 cases and no effect in the other. Gastrin and gastrin-like tetrapeptide (NK-T), and oxytocin in $0.1 \mu\text{g}$ produced no response. Cholecystokinin caused a powerful contraction of the canine gall bladder in 5 out of 6 cases, and was about 10 times more potent than bradykinin. Chlorobutanol used as preservative of lys-vasopressin had no effect on the gall bladder at the concentration used for administration of the drug.

b) *Effect on the vascular bed.* Bradykinin, eledoisin, kallikrein, gastrin and gastrin-like tetrapeptide, and oxytocin produced a vasodilation. Lys-vasopressin and angiotensin constricted the artery, while cholecystokinin dilated it slightly in 4 out of 6 cases and caused no response in the others.

4) Ganglion stimulating agents (Figs. 6 and 7).

a) *Effect on the contractility of the gall bladder.* Nicotine, TMA, McN-A-343 and lobeline contracted the gall bladder. DMPP produced a biphasic response, i. e., a contraction followed by a relaxation in 8 out of 11 cases and a simple contraction in 3 cases. A biphasic response elicited by DMPP was modified by repetitive applications of $10 \mu\text{g}$ as shown in Fig. 7. The relaxation gradually diminished and ultimately disappeared. The initial contraction was rather persistent but finally diminished to a small response.

b) *Effect on the vascular bed.* Ganglion stimulating agents, nicotine, TMA, McN-A-343 and lobeline except DMPP produced a vasodilation. Though the experimental condition was almost the same, DMPP caused variable responses in different animals; a vasodilation, a vasoconstriction, a vasodilation followed by a vasoconstriction, and a vasoconstriction followed by a vasodilation. These vascular responses to DMPP diminished by repetitive applications as shown in Fig. 7.

5) Other biogenic amines (Fig. 8).

a) *Effect on the contractility of the gall bladder.* 5-HT caused an initial contraction followed by a relaxation as did DMPP. Histamine produced a contraction.

Fig. 8. Responses to other biogenic amines. Scales are the same as those in Fig. 3.

Fig. 9. Responses to the adenine and uridine derivatives. Scales are the same as those in Fig. 3.

b) *Effect on the vascular bed.* 5-HT caused a slight vasodilation but in large doses this vasodilation was preceded by a slight vasoconstriction. Histamine produced a vasodilation.

6) *Nucleosides and nucleotides* (Fig. 9).

a) *Effect on the contractility of the gall bladder.* ATP caused a relaxation followed by a contraction, while ADP, AMP and adenosine up to 30 µg did not

Fig. 10. Responses to miscellaneous agents. Scales are the same as those in Fig. 3.

cause any significant response. UTP produced a contraction but UDP, UMP and uridine did not produce any response. TPN and DPN caused no response.

b) *Effect on the vascular bed.* ATP, ADP, AMP, adenosine, TPN and DPN produced a vasodilation. ATP was the most potent and adenosine the weakest. UTP and UDP caused a vasodilation. Other uridine nucleotides had little effect.

7) *Miscellaneous agents* (Fig. 10).

a) *Effect on the contractility of the bladder.* Aminophylline and papaverine caused a relaxation. Ouabain elicited a contraction. CaCl_2 and BaCl_2 produced a contraction, and KCl and MgCl_2 caused a relaxation. Procaine caused no response.

b) *Effect on the vascular bed.* Aminophylline, papaverine and procaine caused a vasodilation, while ouabain did a vasoconstriction. CaCl_2 and BaCl_2 caused a vasoconstriction, while KCl and MgCl_2 produced a vasodilation.

C) *Classification of investigated drugs on the basis of their effects on the contractility of the gall bladder in reference to its vascular bed*

The authors classify the tested drugs to five groups according to their effects on the gall bladder smooth muscle. And drugs of each group are further subdivided into two classes in reference to their vascular effects as shown in Table 2.

Among substances belonging to the first group which produce the contraction of the gall bladder, ouabain, BaCl_2 and CaCl_2 constrict the vascular bed, while choline, ACh, methacholine, bethanechol, carbachol, pilocarpine, bradykinin, eledoisin, kallikrein, cholecystokinin, TMA, McN-A-343, histamine and UTP dilate it. Drugs belonging to the second group produce the relaxation of the gall bladder. Among them, dopamine, noradrenaline, adrenaline, ephedrine, tyramine, lys-vasopressin and TEA produce a vasoconstriction, while isoprenaline, aminophylline, papaverine, KCl and MgCl_2 cause a vasodilation. DMPP, nicotine, lobeline and 5-HT which belong to the third group produce a contraction followed by a relaxation of the gall bladder while they cause a vasodilation. Drugs of the fourth

TABLE 2. *Classification of investigated drugs on the basis of their effects on the gall bladder smooth muscle in reference to its vascular bed*

Effects on contractility of the gall bladder	Vascular responses	Drugs
Contraction	Constriction	BaCl ₂ , CaCl ₂ , ouabain
	Dilation	Choline, acetylcholine, methacholine, carbachol, bethanechol, pilocarpine, bradykinin, eledoisin, cholecystokinin, TMA, McN-A-343, nicotine, lobaline, histamine, UTP
Relaxation	Constriction	Dopamine, noradrenaline, adrenaline, ephedrine, tyramine, lys-vasopressin, TEA
	Dilation	Isoprenaline, aminophylline, papaverine, KCl, MgCl ₂
Contraction followed by relaxation	Constriction	
	Dilation	DMPP, 5-HT
Relaxation followed by contraction	Constriction	Angiotensin
	Dilation	ATP
No effect	Constriction	Phenylephrine, methoxamine
	Dilation	Gastrin, gastrin-like tetrapeptid, oxytocin, ADP, AMP, adenosine, DPN, TPN, UDP, UMP, uridine, procaine

group which cause a relaxation followed by a contraction of the gall bladder are angiotensin and ATP. The former produces a vasoconstriction while the latter dilates the vascular bed. Drugs of the fifth group cause only a vascular response without any effect on the contractility of the gall bladder; a vasoconstriction by phenylephrine and methoxamine and a vasodilation by oxytocin, ADP, AMP, adenosine, TPN, DPN, UDP, UMP and uridine.

DISCUSSION

The gall bladder responds to cholinergic stimulation with contraction, while to adrenergic one with relaxation. Bainbridge and Dale (1905) have reported that the gall bladder responded both to stimulation of the splanchnic nerve and to intravenous administration of adrenaline with either contraction or relaxation. Later investigation showed that a relaxation was elicited with adrenaline in the canine gall bladder *in vivo* (Lieb and McWhorter, 1915) and *in vitro* (Halpert and Lewis, 1930). In the present experiments, dopamine, noradrenaline, adrenaline and isoprenaline caused a relaxation in the majority of cases but phenylephrine and methoxamine known to act mainly on alpha-adrenergic receptors neither contracted nor relaxed the canine gall bladder even with a higher dose up to 10 μ g. Therefore, we conclude that alpha-adrenergic receptors are poorly developed in the canine gall bladder.

TABLE 3. *Classification of various compounds according to the difference of action on the coronary, renal, mesenteric, femoral, vesical, saphenous and cholecystic arteries*

	(a)	(b)	(c)	(d)	(e)	(f)
Coronary artery	Dil.	Dil.	Dil.	Const.	Dil.	Const.
Renal artery	Dil.	Const.	Const.	Const.	Const.	Const.
Mesenteric artery	Dil.	Dil.	Const.	Dil.	Const.	Const.
Femoral artery	Dil.	Dil.	Dil.	Dil.	Const.	Const.
Vesical artery	Dil.	Dil.	Dil.	Const.	Const.	Const.
Saphenous artery	Dil.	Dil.	Const.	Const.	Const.	Dil.
Cholecystic artery	Dil.	Dil.	Various	Const.	Const.	Dil.
	ATP ADP UDP Bradykinin ACh Histamine Isoprenaline Papaverine Theophylline	AMP Adenosine DPN UDP	DMPP Nicotine Lobeline	TEA Procaine	Adrenaline Noradrenaline Ephedrine 5-HT	Angiotensin Lys-vasopressin Methoxamine Ouabain UMP

Ivy and Oldberg (1928) first found that the gall bladder responded with a significant contraction to a gastrointestinal hormone which they named as cholecystokinin. Halpert and Lewis (1930), however, reported negative results for cholecystokinin in experiments with the isolated gall bladder of the dog. Jung and Greengard (1933) carried out the experiments with the isolated gall bladder of the guinea pig and found that the total amount of cholecystokinin needed to produce a contraction was about 50 times larger than the intravenous dose. In the present experiments, the gall bladder sensitively responded with a vigorous contraction to intra-arterial cholecystokinin. Thus, cholecystokinin may probably be secured to have a good access to the smooth muscle from the vascular bed as they suggested.

Lys-vasopressin is known to produce a contraction of the gastrointestinal tract and of its vascular bed. In the present experiments, intra-arterial administration of lys-vasopressin caused a relaxation of the gall bladder, while it constricted the cholecystic artery. The relaxation caused by lys-vasopressin will be characteristic of the smooth muscle of the gall bladder.

DMPP caused a biphasic response, a contraction followed by a relaxation, while it dilated the cholecystic artery. DMPP has a ganglion stimulating action on nicotinic sites in parasympathetic ganglia, while sympathetic nerve endings were also stimulated. The DMPP-induced biphasic response may be ascribed to two actions described above. The response to DMPP was diminished by repeated administrations. Especially, the relaxation was more susceptible than the contraction. Birmingham and Wilson (1965) have reported that DMPP may exert an adrenergic blocking effect on the isolated small intestine by a guanethidine-like action. This may be a probable cause for the disappearance of the relaxation.

Matsumura *et al.* (1968) showed the pharmacological behaviors of the urinary bladder in the dog by means of the intra-arterial administration of various compounds under constant flow perfusion. In comparison with the results of the urinary bladder there were several differences: 1) DMPP and 5-HT caused contraction of the urinary bladder while a biphasic response, a contraction followed by a relaxation, was observed in the gall bladder. 2) ATP and angiotensin produced a contraction of the former, while biphasic response, relaxation followed by contraction, occurred in the latter. 3) Papaverine and aminophylline elicited no response of the former but relaxation of the latter. 4) Lys-vasopressin, TEA and KCl produced contraction of the former but relaxation of the latter. 5) Phenylephrine induced contraction of the former but not any response of the latter.

Recently Yamamoto *et al.* (1970) investigated the responses of the saphenous vascular bed of the dog to various drugs, and supplemented the classification described by Hashimoto and Kumakura (1965). Table 3 shows the present results. According to this classification, all drugs of group (a) also caused a dilation in the cholecystic artery. The drugs of group (b) produced a dilation in the cholecystic artery. In drugs of group (c), nicotine and lobeline caused only a dilation while the effect of DMPP was variable. In drugs of group (d), TEA caused a constrict-

tion of the cholecystic artery likewise of the saphenous, vesical, coronary and renal arteries. Procaine produced a dilation but it constricted the coronary and renal arteries. In drugs of group (e), adrenaline and noradrenaline caused a constriction of the six vascular beds except coronary artery in Table 3. 5-HT caused a constriction of the renal, mesenteric, femoral, vesical and saphenous arteries but a dilation of the coronary and cholecystic arteries.

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