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Regional differences of reactivity to stimulants in the dog portal tree

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1 We studied the regional differences both of reactivity to various stimulants and of neurogenic responses elicited by transmural stimulation in the longitudinal and circular muscles of the truncal portal vein, mesenteric vein, splenic vein and gastric vein of the dog portal tree.

2 Strong spontaneous activity appeared in the longitudinal muscle of the truncal portal vein (96% of preparations tested). Weak spontaneous activity sometimes appeared in the circular muscle of the truncal portal vein (41%) and rarely in the longitudinal muscle of the mesenteric vein (12%). It did not appear in other segments.

3 The splenic vein and the gastric vein showed similar patterns in the relationship between resting tension and response to noradrenaline; that is, the responsiveness of either longitudinal or circular muscle of these two veins increased and then decreased almost parallel as resting tension increased and reached a maximum under the same resting tension.

4 The longitudinal muscle of both the truncal portal vein and the mesenteric vein was more responsive to noradrenaline, acetylcholine, histamine and KCl than the circular muscle; for example 2.02 and 1.44 times more responsive to noradrenaline, respectively. On the other hand, the longitudinal muscle of the splenic vein and the gastric vein responded less well than the circular muscle; for example 0.36 and 0.16 times as responsive to noradrenaline, respectively.

5 Acetylcholine and histamine caused marked contractions which were comparable to those elicited by noradrenaline in the longitudinal muscle of the truncal portal vein. Acetylcholine also elicited similar contractions in the longitudinal muscle of the mesenteric vein but the responses induced in preparations of other segments were small.

6 The longitudinal muscle of the truncal portal vein responded well even to low-frequency stimulation of 2 Hz, while the circular muscles of the truncal portal and splenic veins gave marked responses only to high-frequency stimulation of 10 or 20 Hz or more. These contractile responses were attenuated by phentolamine (10^{-6} M) or atropine (10^{-6} M). The longitudinal muscle of the splenic vein showed no significant response to stimuli of any frequency.

7 It seems that the portal tree receives not only adrenergic but also cholinergic innervation. In addition, the longitudinal muscle of the truncal portal vein may receive non-adrenergic, non-cholinergic innervation as well.

8 The longitudinal muscle of the portal vein may be crucial to venous return in assisting movement of the blood it contains. If this is the case in man, then the regional differences in the portal tree demonstrated in this study may explain why varicose changes during portal hypertension occur preferentially in the oesophagogastric region and rarely in other regions, as blood stasis may occur more readily in the regions of the gastric and splenic veins where the longitudinal muscle is not very active.

Introduction

The oesophagogastric region is known to be particularly susceptible to varicose changes occurring during portal hypertension in man. In order to examine this phenomenon, we supposed that there might be some regional differences of vascular reactivity in the portal tree. The portal vein has long been studied as a model of vascular smooth muscle and its many characteristics have been clarified. The lon-

gitudinal muscle of the truncal portal vein is highly developed (Tsao *et al.*, 1969; Cohen & Wiley, 1977), has rich adrenergic (Docherty & Starke, 1982; Barja & Mathison, 1982) and cholinergic innervation (Sutherland, 1964; Nakazato *et al.*, 1982) and has powerful spontaneous activity (Holman *et al.*, 1968; Hermsmeyer, 1973). However, few studies have been made on other segments of the portal tree or of the differences between the longitudinal and circular muscles.

In this study, the dog portal tree was classified into the truncal portal, mesenteric, splenic and gastric veins. Each vein was divided into longitudinal and circular strips. We examined the regional differences in the pharmacological characteristics between these four veins and the pharmacological similarities between the smooth muscle of the portal vein and that of the gastrointestinal tract. The reason for the susceptibility of the oesophagogastric region to varicose changes during portal hypertension in man are discussed in relation to the results.

Methods

Portal trees from adult mongrel dogs of either sex, weighing 8 to 21 kg, were used. The animals were anaesthetized with pentobarbitone sodium (25 mg kg^{-1}, i.v.) and killed by cutting both carotid arteries. The portal tree from the hepatic hilus to the edge of the gastrointestinal tract or the splenic hilus was removed and separated into the truncal portal vein (which ranged from the confluence of the splenic vein to the hepatic bifurcation), mesenteric vein (which was distal to the liver relative to the confluence of the splenic vein), splenic vein and gastric vein. These four veins were separated 5 mm distal from the origin of the first branch, and cut longitudinally or circularly. All strips were prepared to be of the same size, 2 mm in width and 15 mm in length, under a dissecting microscope. The strips were hung vertically between a stationary supporting Lucite-rod and a force-displacement transducer (Nihon Koden Kogyo Co., Tokyo, Japan), and mounted in organ baths containing 20 ml of Krebs-Henseleit solution of the following composition (mM): NaCl 118, KCl 4.7, $CaCl_2$ $2H_2O$ 2.5, KH_2PO_4 1.2, $MgSO_4$ $7H_2O$ 1.2, $NaHCO_3$ 23.3, glucose 10, made up in distilled and deionized water. The bath medium was maintained at 37°C, pH 7.4, and aerated before and during experiments with 95% O_2 and 5% CO_2. At the start, a resting tension of 1 g was applied to all strips. These preparations were equilibrated for 100 min during which time the bath solution was changed every 20 min.

Changes of muscle tension were recorded isometrically on a polygraph. Spontaneous activity was studied and responses to noradrenaline were measured during stepwise increases in the resting tension from 0.5 to 5.0 g. Noradrenaline was used as a representative vasoactive agonist and was added to the bath cumulatively from 10^{-8} to 10^{-4} M.

In later experiments, the resting tension was fixed at 2 g for all preparations. Noradrenaline, acetylcholine, histamine and KCl were added cumulatively from 10^{-8} to 10^{-4} M, 10^{-8} to 10^{-3} M, 10^{-8} to 10^{-4} M and 10^{-2} to 7×10^{-2} M, respectively. Four kinds of agonists were administered to the same preparation in turn and the bath solution was changed three times every 20 min between the application of different agonists.

Electrical transmural stimulation was performed on the longitudinal and circular muscles of the truncal portal vein and the splenic vein. Stimulus-parameters were 0.3 ms duration, 50 V intensity and frequencies of 2, 5, 10, 20 and 40 Hz were applied for 10 s.

Statistics

Student's paired *t* test was used to analyse the inhibitory effects of phentolamine and atropine. Student's paired *t* test was used to analyse the differences in contractions and EC_{50}s between the longitudinal and circular muscles. Data are presented as the mean ± s.e.mean. The value in Tables 2 and 3 are expressed as the ratio of mean values.

Drugs

The following drugs were used: noradrenaline hydrochloride, histamine dihydrochloride, potassium chloride and diphenhydramine hydrochloride (Nakarai Chemicals Co.); acetylcholine chloride, atropine sulphate, choline chloride and physostigmine sulphate (Wako Pure Chemical Industries Co.); phentolamine mesylate (Ciba-Geigy); tetrodotoxin (Sigma Chemicals).

Results

Spontaneous activity of the portal tree

Spontaneous activity was observed in 96% of the longitudinal muscle preparations (out of 48) and 41% of the circular muscle preparations (out of 39) of the truncal portal vein, but in only 12% of the longitudinal muscles of the mesenteric vein (out of 17). No spontaneous activity occurred in either the circular muscle preparations of the mesenteric vein or in muscle of the splenic and gastric veins. When compared with spontaneous activity of the longitudinal muscle of the truncal portal vein, the circular muscle of the truncal portal vein and the longitudinal muscle of the mesenteric vein developed less tension.

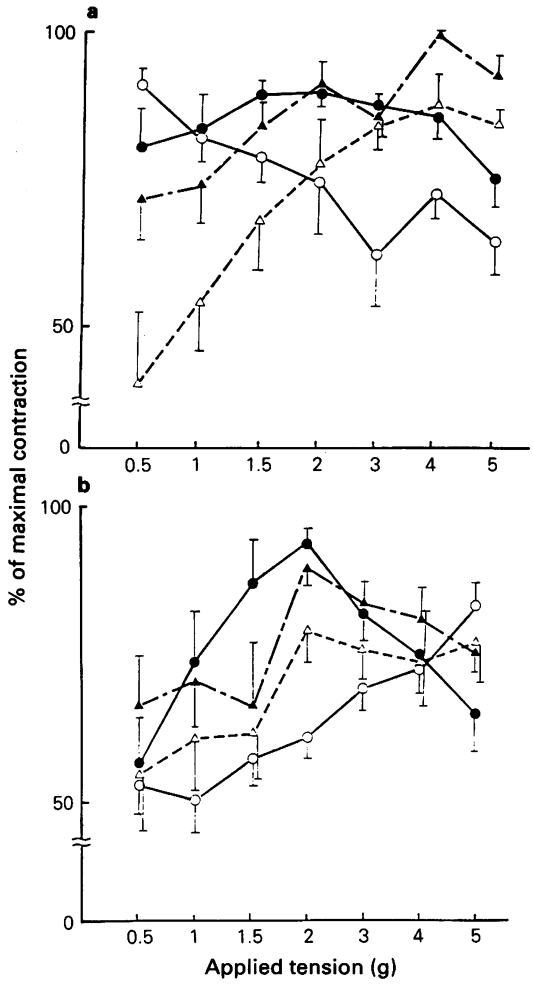

Figure 1 Relationships between applied tension and contraction of the longitudinal (a) and circular (b) muscles of four portal segments to noradrenaline (10^{-5} M) when applied tension was changed stepwise from 0.5 to 5.0 g. Ordinates indicate the percentage of the maximal contraction of each preparation elicited by noradrenaline (10^{-5} M). Abscissae show applied tensions. Vertical lines show s.e.mean. $n = 5$ experiments for both muscles of each segment. (○) Truncal portal vein, (●) mesenteric vein, (△) splenic vein, (▲) gastric vein.

The relationship between resting tension and response to noradrenaline

Contractile responses to noradrenaline were examined as resting tension was changed from 0.5 to 5.0 g stepwise. Figure 1a and b shows the contractile responses to noradrenaline (10^{-5} M) in the longitudinal and circular muscle preparations of each segment. Noradrenaline at a concentration of 10^{-5} M elicited submaximal contractile responses in the veins examined. In the longitudinal muscles (Figure 1a), the responsiveness of the truncal portal vein decreased gradually as resting tension increased. On the other hand, that of the mesenteric vein increased up to the maximal response under a resting tension of 2 g, and thereafter decreased. Both the splenic and gastric veins showed maximal responses under a resting tension of 4 g. In the circular muscles (Figure 1b), the responsiveness of the truncal portal vein increased with increase of resting tension. All preparations of the mesenteric, splenic and gastric veins showed maximal responses under a resting tension of 2 g. In particular, the two curves obtained for the splenic and gastric veins were in good agreement in both muscle layers. Similar results were also obtained in response to noradrenaline (10^{-6} M).

Regional differences in responses to noradrenaline, acetylcholine, histamine and KCl

Resting tension was fixed at 2 g for these experiments. Figure 2 shows the absolute values of the maximal contractile response of each segment in the portal tree to noradrenaline, acetylcholine, histamine and KCl. In the case of the response to noradrenaline, the truncal portal vein exhibited a marked contractile response, especially the longitudinal muscle. The order of responsiveness was as follows: truncal portal vein > mesenteric vein > splenic vein > gastric vein. This tendency was prominent in the longitudinal muscle and was not so marked in the circular muscle. In the truncal portal and mesenteric veins, the longitudinal muscle was more responsive than the circular one and in the splenic and gastric veins, the circular muscle was more responsive than the longitudinal muscle preparations.

When the responses to acetylcholine were examined, the truncal portal vein and the mesenteric vein exhibited strong contractile responses comparable to those to noradrenaline, especially in the longitudinal muscle, but the splenic vein and the gastric vein did not exhibit such strong contractions.

The longitudinal muscle of the truncal portal vein exhibited as strong a response to histamine as that to noradrenaline. Smaller responses to histamine were observed in other segments.

The truncal portal vein and the mesenteric vein exhibited markedly weaker responses to KCl in both muscle layers when compared with those to noradrenaline and acetylcholine. The responses of the splenic vein and the gastric vein to KCl in either muscle layer were weaker than those to noradrenaline, but as strong as those to acetylcholine.

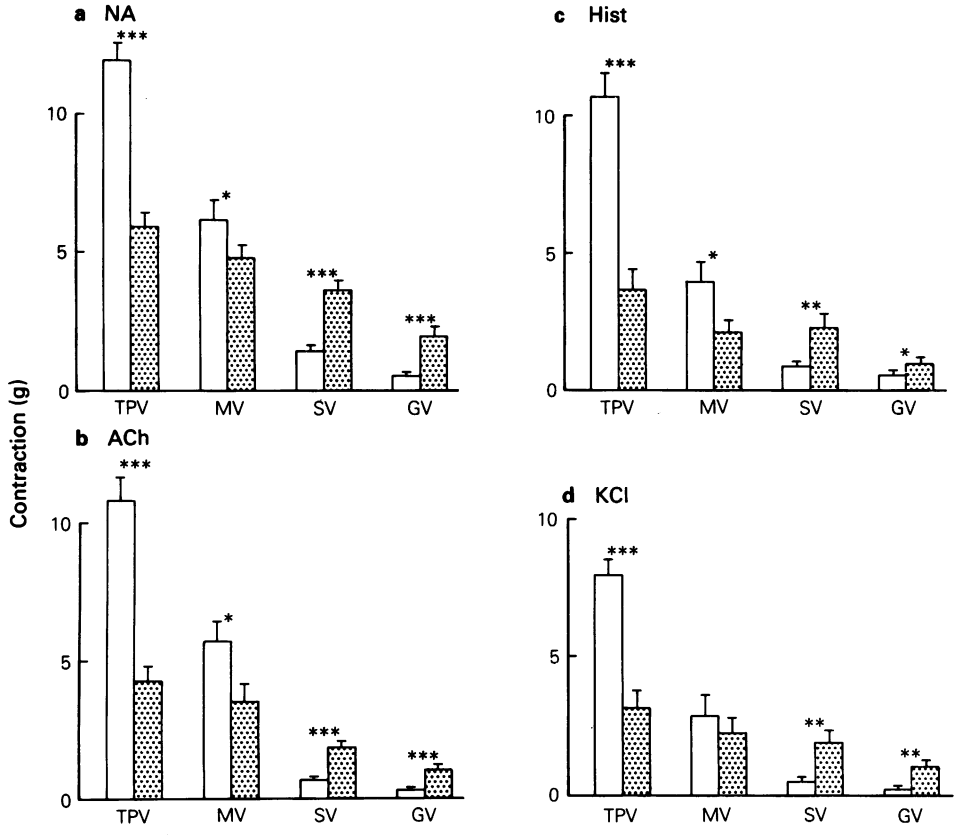

Figure 2 Mean values of contractions of four portal segments to noradrenaline (NA) 10^{-4} M (a), acetylcholine (ACh) 10^{-3} M (b), histamine (Hist) 10^{-4} M (c) and KCl 7×10^{-2} M (d). Open columns and stippled columns represent the longitudinal muscles (long) and the circular muscles (circ), respectively. Vertical lines show s.e.mean. $*P < 0.05$, $**P < 0.025$, $***P < 0.001$ between the longitudinal and circular muscles. Abbreviations are: TPV, truncal portal vein; MV, mesenteric vein; SV, splenic vein; GV, gastric vein. The numbers of experiments were: TPV long 14, circ 15; MV long 9, circ 11; SV long 12, circ 14; GV long 10, circ 13.

Table 1 shows the EC_{50} values for both muscle layers in each portal segment to the four stimulants. All preparations were highly responsive to noradrenaline and the longitudinal muscles of the truncal portal and mesenteric veins were more responsive to acetylcholine, histamine and KCl than other segments. In the truncal portal and mesenteric veins, there were significant differences in responsiveness between the longitudinal and circular muscles to noradrenaline, acetylcholine and histamine but a difference was observed to KCl only in the truncal portal vein.

Table 2 shows the ratios of contractions to stimulants, applied at concentrations giving maximal responses, between the longitudinal and circular muscles of each segment. In the truncal portal and mesenteric veins, the longitudinal muscle was more responsive to all stimulants than the circular muscle. The reverse was the case in the splenic and gastric veins.

Table 3 shows the ratios of the maximal contractions elicited by acetylcholine, histamine and KCl to the contractions induced by noradrenaline in all segments. The longitudinal muscle of the truncal portal vein was highly responsive to acetylcholine and histamine compared to noradrenaline whereas, the longitudinal muscle of the mesenteric vein was highly responsive only to acetylcholine compared to noradrenaline.

Regional differences of neurogenic responses

The preparations were classified into two groups from the results obtained in the above sections. One group consisted of the truncal portal and mesenteric veins

Table 1 EC_{50} values for both muscle layers in each portal segment to noradrenaline, acetylcholine, histamine and KCl

		NA	*ACh*	*Hist*	*KCl*
Truncal portal vein	long	-6.74 ± 0.12***	-5.83 ± 0.15**	-6.23 ± 0.15***	-1.84 ± 0.10**
	circ	-6.01 ± 0.06	-5.36 ± 0.11	-4.85 ± 0.12	-1.47 ± 0.02
Mesenteric vein	long	-6.49 ± 0.14**	-6.62 ± 0.12**	-5.15 ± 0.20*	-1.63 ± 0.06
	circ	-6.15 ± 0.05	-5.92 ± 0.13	-4.64 ± 0.15	-1.52 ± 0.07
Splenic vein	long	-6.10 ± 0.04*	-5.27 ± 0.11	-4.74 ± 0.12	-1.49 ± 0.03
	circ	-6.31 ± 0.09	-5.21 ± 0.11	-4.84 ± 0.14	-1.52 ± 0.04
Gastric vein	long	-6.30 ± 0.10	-5.14 ± 0.07	-5.12 ± 0.22	-1.51 ± 0.03
	circ	-6.23 ± 0.04		-4.69 ± 0.13	-1.47 ± 0.04

Values are presented as log mean $EC_{50} \pm$ s.e. for noradrenaline (NA), acetylcholine (ACh), histamine (Hist) and KCl. * $P < 0.05$, ** $P < 0.025$, *** $P < 0.001$ between the longitudinal (long) and circular (circ) muscles. The numbers of experiments are the same as in Figure 2.

Table 2 Ratios of contractions between the longitudinal and circular muscles of four portal segments

	Truncal portal vein	*Mesenteric vein*	*Splenic vein*	*Gastric vein*
NA	2.02	1.28	0.40	0.30
ACh	2.50	1.61	0.38	0.32
Hist	2.94	1.87	0.39	0.36
KCl	2.51	1.25	0.27	0.28

The ratios of mean contractions between the longitudinal and circular muscles of four portal segments to noradrenaline (NA) 10^{-4} M, acetylcholine (ACh) 10^{-3} M, histamine (Hist) 10^{-4} M and KCl 7×10^{-2} M, are shown.

that had longitudinal muscles highly responsive to stimulants. The other group consisted of the splenic and gastric veins that had longitudinal muscles less responsive to stimulants. Transmural stimulation was applied to the truncal portal and splenic veins. Figure 3 shows the representative recordings of the contractile responses of both muscle layers of these two veins to transmural stimulation from 2 to 40 Hz. Atropine (10^{-6} M) was administered first and subsequently phentolamine (10^{-6} M) was added. The residual responses disappeared completely after tetrodotoxin (3×10^{-7} M). Figure 4 shows the absolute values of the contractile responses of the four preparations to KCl (3×10^{-2} M) and transmural stimulation from 2 to 40 Hz. Contractile responses elicited by KCl (3×10^{-2} M) corresponded to 84, 69 and 80% of the maximal responses to transmural stimulation in the longitudinal and circular muscles of the truncal portal vein and the circular muscle of the splenic vein, respectively. The longitudinal muscle of the truncal portal vein exhibited a 4.86 ± 0.65 g contractile response to the stimulus of 2 Hz, which was equivalent to 69% of the maximal response (7.07 ± 0.67 g). The circular muscle of the truncal portal vein exhibited a 0.98 ± 0.23 g response to the stimulus of 5 Hz, which was equivalent to 30% of the maximal response (3.30 ± 0.56 g). The circular muscle of the splenic vein exhibited no significant response to stimuli of either 2

Table 3 Ratios of contractions induced by acetylcholine, histamine and KCl to that elicited by noradrenaline

		Truncal portal vein	*Mesenteric vein*	*Splenic vein*	*Gastric vein*
ACh / NA	long	0.90	0.92	0.48	0.57
	circ	0.73	0.73	0.51	0.53
Hist / NA	long	0.90	0.64	0.60	0.60
	circ	0.61	0.44	0.63	0.50
KCl / NA	long	0.66	0.46	0.35	0.48
	circ	0.53	0.47	0.52	0.52

The ratios of mean contractions induced by acetylcholine (ACh) 10^{-3} M, histamine (Hist) 10^{-4} M and KCl 7×10^{-2} M to the contraction elicited by noradrenaline (NA) 10^{-4} M in four portal segments are shown, long and circ represent longitudinal and circular muscles, respectively.

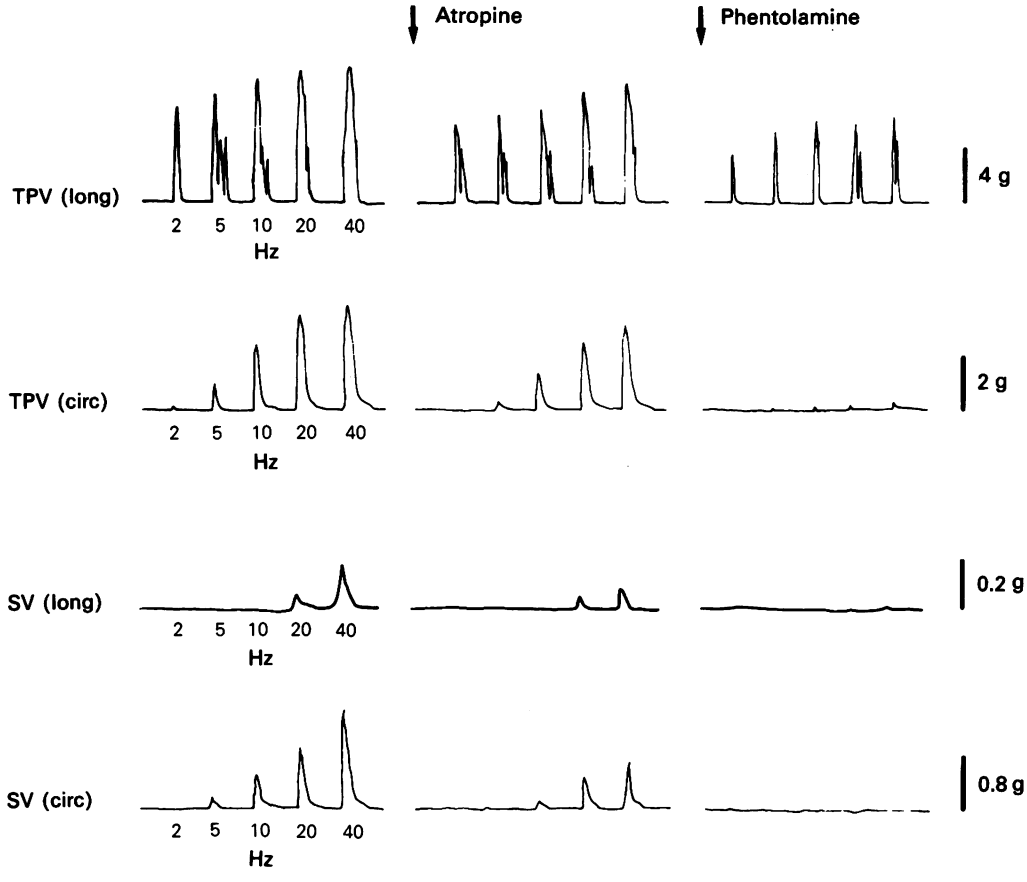

Figure 3 Representative recordings of contractile responses of the longitudinal (long) and circular (circ) muscles of the truncal portal (TPV) and splenic (SV) veins to transmural stimulation from 2 to 40 Hz. Atropine (10^{-6} M) was administered first and then phentolamine (10^{-6} M) was added.

or 5 Hz, but gave a 0.43 ± 0.07 g response to 10 Hz, which was equivalent to 29% of the maximal response (1.47 ± 0.16 g). The longitudinal muscle of the splenic vein showed a negligible response to the stimuli of any frequency.

Figure 5 shows the inhibitory effects of phentolamine (10^{-6} M) and atropine (10^{-6} M) on the contractile responses to transmural stimulation. Phentolamine suppressed moderately the contractile response in the longitudinal muscle of the truncal portal vein and markedly decreased it in the circular muscles of the truncal portal and splenic veins. Atropine slightly suppressed the contractions in the longitudinal muscle of the truncal portal vein, but reduced them to a greater extent in the circular muscles of the truncal portal and splenic veins. All these effects of either phentolamine or atropine were significant with $P<0.005$. After simultaneous administration of phentolamine and atropine, about 60% of the response remained in the longitudinal muscle of the truncal portal vein, but only 10% in the circular muscle of the truncal portal vein and the response almost disappeared in the circular muscle of the splenic vein. When choline (10^{-5} M) and physostigmine (3×10^{-6} M) were added simultaneously to the bathing media of different preparations the contractile responses were not enhanced significantly in any of the preparations. In addition, diphenhydramine (10^{-6} M) had no inhibitory effect on the contractile responses.

Discussion

The portal vein is noted as a unique vein. Most arterial or venous muscles are composed of mainly circular

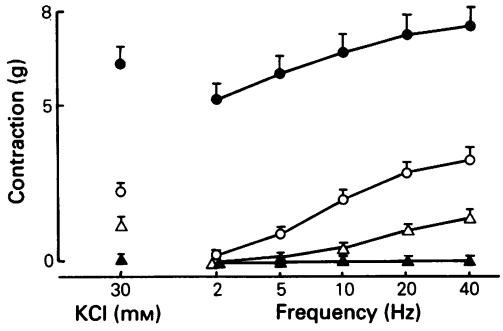

Figure 4 Mean values of contractions of the longitudinal and circular muscles of the truncal portal and splenic veins to KCl (3×10^{-2} M) and transmural stimulation (from 2 to 40 Hz). Vertical lines show s.e.mean. The symbols and the numbers of experiments are as follows: (●) longitudinal muscle of the truncal portal vein ($n = 12$), (○) circular muscle of the truncal portal vein ($n = 10$), (▲) longitudinal muscle of the splenic vein ($n = 6$), (△) circular muscle of the splenic vein ($n = 8$).

muscle layers with little or no muscle arranged longitudinally although there are several exceptions including the coronary and pulmonary arteries (Furchgott, 1955) and the renal and femoral veins (Cohen & Wiley, 1977). However, the portal veins of many species have inner circular and outer longitudinal bilayer structures consisting of smooth muscle cells, and these show spontaneous activity (Homan *et al.*, 1968; Hermsmeyer, 1973; Cohen & Wiley, 1977). Spontaneous activity of the truncal portal vein is myogenic and spreads from the mesenteric end to the hepatic end (Johanson & Ljung, 1967).

In this study, the portal tree was divided into the following four segments, the truncal portal, mesenteric, splenic and gastric veins. Spontaneous activity was almost always observed in the longitudinal muscle of the truncal portal vein. The circular muscle of the truncal portal vein and the longitudinal muscle of the mesenteric vein sometimes showed weak spontaneous activity, whereas other segments did not. Although the functional role of the spontaneous activity of the portal vein is not clear, that of the gastrointestinal tract is related to active transport of its contents

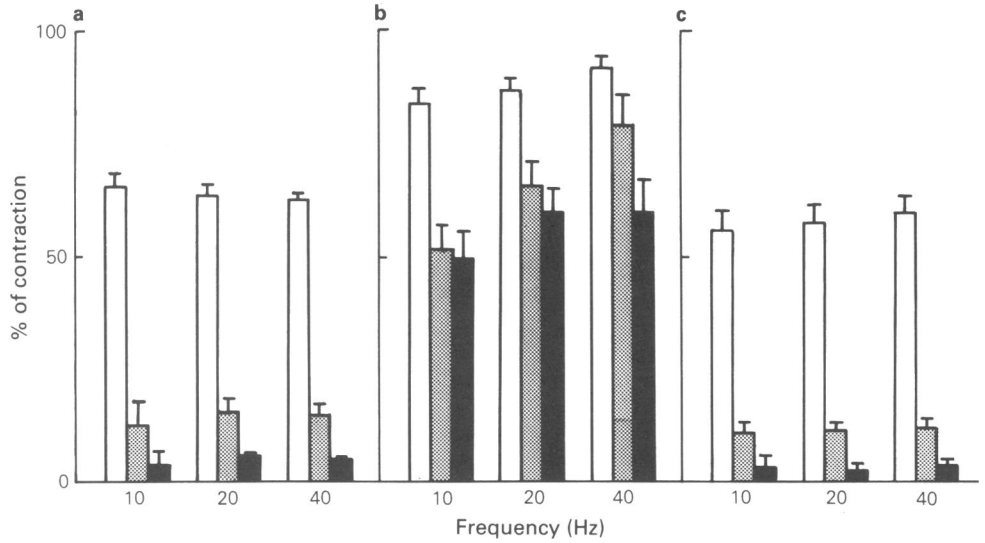

Figure 5 Inhibitory effects of phentolamine and atropine on contractions of the longitudinal and circular muscles of the truncal portal vein and the circular muscle of the splenic vein to transmural stimulation of 10, 20 and 40 Hz. Ordinates indicate the percentage of the contraction obtained relative to control contractions elicited before administration of antagonists. Open columns represent longitudinal muscle (long) of the truncal portal vein (TPV); stippled columns: circular muscle of the truncal portal vein; solid columns: circular muscle of the splenic vein (SV). Vertical lines show s.e.mean. Each reduction in the contractile response induced by phentolamine or atropine was significant ($P < 0.005$). (a) Phentolamine (10^{-6} M) was administered, (b) atropine (10^{-6} M) was administered, (c) phentolamine (10^{-6} M) and atropine (10^{-6} M) were administered simultaneously. The numbers of experiments are as follows: (a) TPV long 12, circ 12; SV circ 12; (b) TPV long 12, circ 10; SV circ 7; (c) TPV long 10, circ 13, SV circ 9.

(Melville *et al.*, 1975; Anuras *et al.*, 1979; Magagno & Christensen, 1981). It is assumed that spontaneous activity of the portal vein also participates in the transport of the blood it contains.

Some studies have demonstrated that the splenic and gastric veins have different characteristics relative to other portal segments when examined pharmacologically or embryologically. In the dog, the splenic vein has a high sensitivity to noradrenaline and 5-hydroxytryptamine, like the veins of the body wall or extremities, and is not so sensitive to histamine unlike the main portal or mesenteric veins (Ishikawa *et al.*, 1980). The gastric vein is said to be derived embryologically from the foregut plexus, while another portal segment derived from the vitello-umbilical veins (Butler, 1952) and the splenic vein is a shunt vein between the spleen and the portal system (Miki, 1983). From our study concerning the resting tension-response relationship, the splenic and gastric veins had common features and differed from the truncal portal and mesenteric veins. This result also implies that the splenic and gastric veins are able to be distinguished from other portal segments.

In many species the longitudinal muscle of the portal vein is well developed and its circular muscle is relatively underdeveloped in either the pharmacological or the anatomical sense; that is, the longitudinal muscle is several times as thick as the circular muscle, rich in such intracellular elements as vasavasorum, pinocytotic vesicles or mitochondria, and exhibits stronger responses to vasoactive substances than the circular muscle (Holman *et al.*, 1968; Tsao *et al.*, 1969; Hall & O'Connor, 1973; Carvalho & Rodrigues, 1978). However, most of these studies were limited to the truncal portal vein. We studied the response of each portal segment to noradrenaline, acetylcholine, histamine and KCl. All segments responded with a contraction to these four agonists and the pharmacological predominance of the longitudinal muscles of the truncal portal and mesenteric veins may have some functional significance.

The truncal portal vein has not only rich adrenergic innervation but also abundant cholinoceptors and probably cholinergic innervation (Hughes & Vane, 1967; Nakazato *et al.*, 1982; Taniguchi *et al.*, 1983). It was demonstrated that the longitudinal muscle of the rabbit truncal portal vein responded to 10^{-5} M acetylcholine about four times as intensely as its circular muscle, and that the responsiveness of both muscles to histamine was almost equal. This contractile response was mediated by the H_1-histamine receptor (Brown *et al.*, 1982). Our findings regarding the response to acetylcholine indicate that functional cholinoceptors are abundant in the truncal portal and mesenteric veins, especially in the longitudinal muscles, and sparse in the splenic and gastric veins. From the results obtained, the functional histamine receptors appear to be abundant in the longitudinal muscles of the truncal portal and mesenteric veins and relatively lacking in other veins. The high responsiveness of the longitudinal muscles of the truncal portal and mesenteric veins to acetylcholine and histamine reminds us of the characteristics of the smooth muscle of the gastrointestinal tract.

In general, the main innervation of the gastrointestinal smooth muscle is cholinergic, and that of the vascular smooth muscle is adrenergic. Most vascular smooth muscles are not innervated by cholinergic fibres but there are several exceptions, for example, the middle segment of the dog inferior vena cava (Nakazato *et al.*, 1982). From our observations of the responses to electrical transmural stimulation, the smooth muscle of the portal vein seems to be innervated not only by adrenergic but also by cholinergic fibres. In addition, the longitudinal muscle of the truncal portal vein may have non-adrenergic, non-cholinergic innervation. These facts also suggest similarities in the smooth muscles between the portal vein and the gastrointestinal tract. These similarities may indicate a functional role for the longitudinal muscle of the truncal portal vein that is highly innervated.

In conclusion, we suggest that the portal vein, especially its longitudinal muscle, shares some of the characteristics of the smooth muscle of the gastrointestinal tract which actively transports its contents. The longitudinal muscle of the portal vein may take part in the active transport of its contents. If this is the case in man, blood stasis may occur more easily, with an increase of pressure, in the regions of the splenic and gastric veins where the longitudinal muscle is not extensively developed compared with other regions.

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