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Effects of Solvents and Detergents on the Contractions of Isolated Smooth Muscle Preparations

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Abstract—In testing poorly soluble substances in-vitro on isolated organs, organic solvents and solubilizers are used to increase water-solubility. To facilitate selection of appropriate substances, the effects of eleven of these chemicals have been studied in the following isolated smooth muscle preparations: guinea-pig ileum stimulated by carbachol, histamine, 5-HT or single field stimuli; rat fundus stimulated by 5-HT; and mouse vas deferens stimulated by noradrenaline or trains of field stimuli. Nine solvents (acetone, diethyleneglycol monoethylether, dimethyl sulphoxide, ethanol, glycerol, methanol, polyethylene glycol 400, 1,2-propanediol, Tetraglycol (tetrahydrofurfurylalcohol polyethyleneglycolether)) and two detergents (Triton-X 100 and Tween 80) were examined. The vas deferens proved to be most resistent, whereas rat fundus and guinea-pig ileum were more sensitive to the effects of solvent when present from 1 to 10 g L^{-1}. Most solvents caused non-specific, concentration-dependent reversible inhibition of contractions. Dimethyl sulphoxide in high concentrations increased the contractile responses of guinea-pig ileum stimulated by 5-HT and in both experiments with electrical stimulation. Polyethylene glycol 400 augmented the response of mouse vas deferens to electrical stimulation. Overall, 1,2-propylene glycol and polyethylene glycol 400 had the least effect and can be used in a concentration of 3 g L^{-1}, and in qualitative studies even up to 10 g L^{-1}. Glycerol, both monohydric alcohols and dimethyl sulphoxide produced more intense effects and should not exceed concentrations of 1–3 g L^{-1}. Stronger inhibition was caused by diethyleneglycol monoethylether, acetone and Tetraglycol, and the bath concentrations of these substances should not exceed 0·5–1g L^{-1}. Of the detergents only Tween 80 is suitable as a solubilizer in smooth muscle preparations in-vitro, forming micelles at 10 mg L^{-1} a concentration tolerated by isolated organs in this study.

In physiological and pharmacological experiments on isolated organs a major problem is often insufficient solubility of substances used. Besides the formation of salts the most popular method of increasing solubility is the use of solubility mediating substances. An increased solubility in water can be obtained by the use of hydrotropic solvents, formation of water soluble complexes or occlusion compounds or solubilization with detergents in micellar solutions. A survey of twelve pharmacological journals for 1985 revealed the most commonly used solvents in isolated organ preparations were acetone, diethyleneglycol monoethylether (DGMEE), dimethyl sulphoxide (DMSO), ethanol, glycerol, methanol, polyethylene glycol 400 (PEG 400) and 1,2-propanediol. To this list of hydrotropic solvents were added tetrahydrofurfurylalcohol polyethyleneglycolether and the detergents, Triton-X 100 and Tween 80. The effects of these chemicals were examined in experiments with three isolated smooth muscle preparations. A comparable study was made by Budden et al (1978a, b, c), however, only some of the solvents used in the present study were studied and only on the guinea-pig ileum stimulated by histamine, carbachol or $BaCl_2$.

Materials and Methods

General

The animals were stunned by a blow on the neck and killed by exsanguination. The organs were removed immediately and suspended in nutrient solution for further preparation. Guinea-pig ileum and rat fundus were suspended in magnesium-free Tyrode solution, the vas deferens in modified Krebs solution. The nutrient solutions were kept at 37°C and saturated with carbogen (95% O_2 and 5% CO_2). The experiments with electrically stimulated ileum preparations were carried out in organ baths containing 20 mL with fixation hooks and ring electrodes made of stainless steel (V_2A) while all the others were conducted with organ baths of 5 mL capacity with mounting installations and ring electrodes made of platinum.

Mechanical responses were recorded using Isometric Muscle Transducers, Model 363, Electronic Recording Module, Model 350, and a Speed Chart Mover, all of Harvard Apparatus, Millis, USA. Rectangular pulses for field stimulation were applied with a stimulator 215/II, Hugo Sachs Elekronik KG, Hugstetten, Germany.

The experiments were started after an equilibration period of 90 min. The interval between two stimulations was 15 min. Most tests were conducted with six preparations each.

The preparations

Guinea-pig ileum. Guinea-pigs, 900–1200 g, from a strain raised in this laboratory were used. With two cuts, 10 and 30 cm from the aboral end, the terminal section of the ileum was removed and 2 cm strips were mounted in the organ baths. One gram initial resting tension was applied to the tissues.

Rat fundus. Wistar rats (Bor: WISW), 180–250 g, were used. The fundus was separated from the whole stomach prep-

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aration and cut longitudinally into strips 15 mm long and 3–4 mm in diameter. Thread was tied to the strips and the preparations were installed in the organ baths under a resting tension of 1 g.

Mouse vas deferens. Both vasa deferentia of male NMRI mice (Crl: NMRI), 30–36 g, were removed in their entire length from the epididymis to the seminal vesicle and stripped of adhering tissue. The seminal contents were flushed out of the ductus lumen by gently pressing along the preparation. Thread was tied to the ends of the vas deferens and both ends were connected so that the preparation formed a loop. This loop was fixed by a platinum hook in the 5 mL organ bath. A resting tension of 0·5 g was applied to the preparations. Electrical stimulation was between the platinum hook and a ring electrode of platinum fixed 1 cm above the organ.

Stimuli and response

For the study of solvent effects, contractions were induced with submaximal stimuli. The dose-response correlation was examined in preliminary experiments. The mechanical responses of the ileum to carbachol (3×10^{-7} M = EC65–75), histamine (2.17×10^{-7} M = EC45–75) or 5-HT (1.1×10^{-6} M = EC65–75) reached the maximum in 4 to 8 s after administration of the respective spasmogen. Single field stimuli for 0·5 ms at 20 s intervals with 10 V generated short submaximal contractions with an almost instantaneously occurring maximum. The electrical stimulation was applied via the fixation hook and a stainless steel ring installed above the preparation. The mechanical response of the fundus to stimulation with 5-HT (1.1×10^{-7} M = EC40–70) proceeded as a prolonged ascent of contraction force with a maximum 1–3 min after application.

The vasa deferentia were stimulated with 9.7×10^{-5} M noradrenaline (NA). Although the concentration of the spasmogen was relatively high (EC84–96) this dose was chosen because it produced sufficient contraction amplitudes. After administration of NA the preparations reacted with an initial almost immediate maximum followed by a second one, 10–20 s later. NA administrations of equal dose in successive experimental periods on the same vas deferens produced initial maxima with varying amplitudes, whereas the secondary mechanical response was constant. Therefore this secondary maximum was taken as contractile response representative of concentration. In the second experimental set with this preparation, trains of field stimuli (25 V, 20 s^{-1} and 0·5 ms duration every 30 s for 0·5 s) were applied through the fixation hook and a platinum ring electrode; this stimulation was submaximal. The contractions on electrical stimulation of the ileum and vas deferens could be abolished by administration of tetrodotoxin (0·3 μM).

Drugs and solutions

The chemical and physical data and the origin of the substances used are listed in Table 1. The other chemicals were: carbachol (Fluka, Buchs, Switzerland), histamine dihydrochloride (Merck, Darmstadt, Germany), 5-hydroxytryptamine creatinine sulphate (Sigma, St. Louis, USA), noradrenaline hydrochloride (Synochem, Hamburg, Germany) and tetrodotoxin (Sigma, St. Louis, USA). All drugs were dissolved and diluted with 0·9% w/v NaCl (saline). Final bath concentrations refer to the base.

Magnesium-free Tyrode solution consisted of (mM): NaCl 136·8; KCl 2·7; $CaCl_2$ 1·8; $NaHCO_3$ 11·9; NaH_2PO_4 0·42; D-glucose 5·55, and modified Krebs solution (mM): NaCl 118; KCl 4·75; $CaCl_2$ 2·5; $NaHCO_3$ 25·0; KH_2PO_4 1·21; D-glucose 11·11 and L-tyrosine 0·25 in experiments with electrical stimulation.

Measurement and statistics

Contractions of the isolated preparations induced by the spasmogens or periodical electrical stimulations served as controls. Each injection of a solvent was followed by a control reaction (without solvent), so that complete recovery could be assured. The effect of the solubility-mediating substances was measured by comparing controls with contractions provoked after 2 min incubation with the respective solvent. The solvents could be washed out so that up to three of these substances were tested on the same preparation, provided the control contraction height was regained after the wash-out. Administration of detergents caused irreversible damage to the isolated organs so that experiments with Triton-X 100 or Tween 80 were performed at the end. The concentration range of the chemicals tested was determined in preliminary experiments. All solvents were administered in doses with final bath concentrations of 1, 3·3 and 10 g L^{-1}. The detergents were also added in logarithmic steps from 0·1 to 10 mg L^{-1} for Triton-X 100 and from 10 mg L^{-1} to 3·3 g L for Tween 80. For statistical evaluation the signed rank test for paired replicates (Wilcoxon) was performed with a P value of $< 0{\cdot}05$ as the criterion for statistical significance.

Table 1. Solvents and detergents studied for their effect on isolated smooth muscle preparation.

Solvent	Mol.wt	Specific gravity [d20°C, *d25°C]	Purity	Origin
Acetone	58·08	0·788*	p. analys.	Merck, Darmstadt
DGMEE	134·18	0·999*	p. synth.	Merck, Darmstadt
DMSO	78·13	1·100	p. spectrosc.	Merck, Darmstadt
Ethanol	46·07	0·789	p. analys.	Merck, Darmstadt
Glycerol	92·09	1.263	DAB	Chem. Fabr. Tempelhof
Methanol	32·04	0·791	p. analys.	Merck, Darmstadt
PEG 400	≈400	1·128*	p. synth.	Merck, Darmstadt
1,2-Propanediol	76·09	1·036	—	Sigma, St. Louis, USA
Tetraglycol	≈201	1·083–1·086	p. synth.	Merck, Darmstadt
Triton-X 100	602·22–646·38	1·06*	p. scint. mes.	Merck, Darmstadt
Tween 80	1296·4	1·08	p. synth.	Merck, Darmstadt

Table 2. Median and range of relative contractions in per cent of controls [n = 6].

Substance	Concn (g L^{-1} or †mg L^{-1})	Guinea-pig ileum			Rat fundus		Mouse vas deferens	
		Carbachol	Histamine	5-HT	Single field stimuli	5-HT	Noradrenaline	Trains of field stimuli
1,2-Propanediol	1	101 (95–105)	100 (97–105)	100 (94–105)	100 (96–100)	99 (96–100)	100 (98–103)	98 (95–100)
	3·3	98 (96–100)	96 (91–100)	95 (92–102)	97 (93–100)	91 (83–98)*	99 (98–103)	96 (91–100)
	10	93 (87–104)	83 (72–93)*	91 (78–98)*	91 (72–107)	78 (66–83)*	95 (90–98)*	93 (89–97)*
PEG 400	1	100 (97–100)	101 (95–103)	100 (94–100)	98 (88–105)	100 (97–102)	100 (100–103)	100 (98–100)
	3·3	97 (92–100)	100 (98–106)	100 (89–104)	92 (67–97)*	96 (92–97)*	100 (97–104)	100 (100–104)
	10	84 (79–91)*	90 (83–92)*	84 (82–93)*	88 (54–93)*	87 (82–92)*	92 (73–94)*	102 (96–115)
Methanol	1	101 (95–103)	100 (92–114)	100 (96–100)	100 (95–103)	100 (97–100)	100 (96–100)	99 (94–100)
	3·3	92 (91–98)*	91 (84–95)*	96 (93–100)	94 (88–100)	100 (97–102)	98 (95–103)	92 (87–97)*
	10	81 (73–85)*	82 (75–87)*	87 (69–93)*	85 (78–90)*	100 (98–109)	90 (84–94)*	86 (79–90)*
Glycerol	1	100 (97–102)	100 (96–100)	100 (98–100)	100 (96–105)	100 (98–100)	100 (98–100)	100 (100)
	3·3	96 (88–98)*	95 (92–100)	94 (88–102)	91 (87–98)*	95 (90–99)*	97 (90–100)	99 (97–100)
	10	81 (71–91)*	80 (75–88)*	75 (71–89)*	75 (43–85)*	89 (83–94)*	88 (71–90)*	93 (87–97)*
DMSO	1	99 (93–103)	100 (90–106)	105 (96–106)	104 (100–128)	100 (98–100)	99 (94–103)	100 (97–100)
	3·3	93 (90–98)*	92 (85–102)	105 (100–110)	112 (109–154)*	92 (88–98)*	97 (93–98)*	100 (96–104)
	10	79 (73–82)*	68 (58–93)*	108 (83–134)[b]	149 (129–232)*	82 (74–89)*	86 (77–90)*	103 (96–107)
Ethanol	1	99 (96–100)	100 (93–105)	100 (100–103)	96 (90–100)	100 (97–100)	100 (97–104)	95 (94–100)
	3·3	92 (88–96)*	96 (94–97)*	93 (87–103)	88 (83–93)*	96 (93–100)	100 (98–111)	94 (93–97)*
	10	67 (59–80)*	78 (71–87)*	77 (64–82)*	68 (42–75)*	84 (75–92)*	92 (89–98)*	80 (65–84)*
Acetone	1	97 (88–100)	97 (86–106)	100 (94–103)	100 (97–104)	96 (93–100)	100 (98–104)	99 (93–100)
	3·3	72 (69–86)*	79 (72–96)*	94 (87–100)	91 (83–100)	76 (64–84)*	98 (89–100)	95 (89–98)*
	10	35 (30–40)*	61 (49–84)*	72 (54–86)*	70 (30–77)*	25 (15–39)*	72 (65–81)*	79 (70–85)*
DGMEE	1	99 (96–100)	98 (96–100)	100 (86–104)	100 (97–111)	96 (93–98)*	99 (94–100)	96 (93–100)
	3·3	86 (72–87)*	82 (73–88)*	100 (93–102)	88 (74–105)	77 (70–84)*	88 (81–95)*	91 (86–99)*
	10	59 (33–62)*	54 (44–63)*	76 (69–83)*	85 (47–110)	38 (28–56)*	63 (58–85)*	76 (71–87)*
Tetraglycol	1	97 (90–100)	98 (95–100)	99 (92–100)	94 (79–102)	95 (93–96)*	100 (95–103)	96 (92–100)
	3·3	79 (71–86)*	78 (73–91)*	86 (80–98)*	85 (65–94)*	81 (65–88)*	85 (76–91)*	92 (86–100)
	10	45 (31–65)*	48 (34–50)*	57 (49–66)*	60 (31–79)*	39 (17–60)*	54 (50–59)*	82 (71–94)*
Tween 80	10	97 (97–100)[a]	100 (95–107)[b]	100 (96–102)[a]	96 (95–100)	—	—	—
	33	88 (86–92)*	84 (73–100)	92 (86–104)	88 (82–95)*	99 (92–100)	96 (91–98)*	94 (91–98)*
	0·1	77 (64–85)*	67 (63–88)*	78 (67–94)*	75 (60–78)*	89 (83–97)*	86 (83–90)*	84 (82–89)*
	3·3	54 (42–67)*	49 (30–62)*	59 (33–73)*	41 (33–53)*	79 (71–94)*	74 (72–80)*	74 (62–77)*
Triton-X 100	0·1†	100 (98–100)[a]	—	—	99 (97–100)	—	—	—
	0·33†	96 (90–98)*	98 (93–100)	100 (97–105)	92 (83–97)*	99 (98–100)	100 (97–103)	97 (94–100)
	1†	80 (69–91)*	84 (69–91)*	91 (84–94)*	83 (45–94)*	97 (93–100)	90 (85–94)*	92 (88–94)*
	3·3†	56 (37–71)*	47 (40–81)*	48 (29–79)*	53 (13–78)*	90 (82–99)*	70 (64–78)*	79 (55–90)*
	10†	—	14 (10–34)*	3 (0–21)*	—	75 (51–90)*	53 (39–63)*	46 (36–65)*

* $P < 0.05$ (Wilcoxon-test for paired data). [a] n = 4, [b] n = 15.

Table 3. EC10 values (g L^{-1}) for decrease or increase of mechanical responses.

	Guinea-pig ileum			Rat fundus		Mouse vas deferens	
	Carbachol	Histamine	5-HT	Field stimulation	5-HT	Noradrenaline	Field stimulation
1,2-Propanediol	> 10	6·5	> 10	> 10†	8·5	> 10	> 10
PEG 400	7·5	10	8·5	4·5	7·5	> 10	> 10*
Glycerol	6	5·5	4·5	3·5	8	9	> 10
Methanol	4	3·5	7·5	5·5	> 10	10	4
DMSO	4·5	3·5	> 10*†	3*	4	8	> 10*
Ethanol	4	6	4·5	2·5	6·5	> 10	6
DGMEE	2·5	4	7	2·5†	1·5	2·5	3·5
Acetone	1·5	2	4·5	3·5	1·5	6	5·5
Tetraglycol	1·5	1·5	2·5	2	2	2·5	4·5
Tween 80	0·025	0·020	0·035	0·025	0·8	0·7	0·6
Triton-X-100	0·0005	0·0007	0·001	0·0005	0·003	0·001	0·001

* Increase of contraction force, † marked variation.

Results

The effects of solvents and detergents are in Table 2 which shows the median values of relative contractions (extreme values in parentheses) in per cent of controls. Table 3 shows the EC10 values for the decrease in mechanical responses. For DMSO and PEG 400, higher concentrations led to increases of contractility. The EC10 values were interpolated by means of approximate curves through the median values.

Discussion

The results demonstrate characteristic differences between the three isolated organs. The mouse vas deferens proved to

Table 4. Recommendation for tolerable concentrations of solvents (g L^{-1}) in quantitative studies on the contractions of isolated guinea-pig ileum, rat forestomach and mouse vas deferens.

	Guinea-pig ileum	Rat fundus	Mouse vas deferens
1,2-Propanediol	2·1	2·8	3·3
PEG 400	1·5	2·5	3·3
Glycerol	1·1	2·6	3·0
Methanol	1·1	3·3	1·3
Ethanol	0·8	2·1	2·0
DMSO	1·0	1·3	2·6
DGMEE	0·8	0·5	0·8
Acetone	0·5	0·5	1·8
Tetraglycol	0·5	0·6	0·8

be most resistant to solvent effects. This is probably due to slow distribution of the substances in the extracellular space because of tight packing of smooth muscle cells (Jones & Spriggs 1975). In comparison with the other preparations the rat fundus showed varying sensitivity according to the substances tested. In proportion to its volume the fundus strip is the preparation with the smallest surface, which possibly may hinder the diffusion of penetrating substances and cause higher resistance to solvent effects. On the other hand the maximum response of the fundus to 5-HT occurs 1–3 min after administration of the spasmogen so that the incubation time with the solvent is prolonged. Moreover the strip represents only a part of the forestomach with uncovered smooth muscle layers, while the other preparations are completely covered with peritoneum and/or mucosa. The guinea-pig ileum with a thin wall and the largest relative surface offers only little resistance to penetrating substances as can be seen by the pronounced reactions to the solvents.

In addition to the morphological differences between the three organs the varying impairment of contractility depends on the different contribution of intrinsic nerves to stimuli transmission. The involvement of neuronal structures was analysed with tetrodotoxin (0·3 μM). The contractile responses of the ileum to 5-HT and the electrical stimulation in both ileum and vas deferens were transmitted completely by nerual structures. Stimulation of the ileum with histamine or carbachol was only partly indirect, 25 and 5%, respectively. The contractions of the fundus stimulated by 5-HT and the vas deferens stimulated by NA were not inhibited by tetrodotoxin.

Glycerol and 1,2-propanediol depressed the reactions to all stimulants and the electrical stimulation to the same degree, whereas both monohydric alcohols seemed to depress the reactions of the vas deferens to electrical stimulation more than to noradrenaline. Their effect on the ileum was uniform and irrespective of the stimulus. The other solvents, acetone, DGMEE, tetraglycol and DMSO, influenced first and foremost the reactions to carbachol and histamine, whereas those to electrical stimulation and 5-HT, being mostly neuronal mediated, were less depressed or, in the case of DMSO even stimulated.

Solvents and detergents affected the contractions at different concentrations depending on their molecular structure and their solubility mediating properties. The solubility-increasing effect of the solvents is thought to be based on a change of the crystalline-like structure of water by reducing the hydrogen bonds between water molecules on the one hand, and on the formation of hydrophobic bonds between the solvent and the substance to be dissolved on the other (Luck 1970). Possibly the impairment of contractility is mostly generated by these mechanisms since a change of configuration of cellular proteins will result in alteration of their biological activity as exemplified by the reversible and non-specific inhibition of bovine erythrocyte cholinesterase caused by DMSO (Sams & Carroll 1966). Furthermore, depending on their lipophilic properties, the solvents will affect the cellular membranes and change the activity of the protein structures indirectly.

Detergents solubilize water-insoluble substances in micelles in colloidal solution. Formation of micelles occurs above the so-called critical micellar concentration (CMC). Detergents affect the reactions of the isolated organs by influencing the cell membranes. Detergent molecules can be incorporated into the membrane and cause a separation of mixed micelles, consisting of detergent and membrane components. Membrane components can also be solubilized directly (Helenius & Simons 1975; Riepl & Vidaver 1978).

For assessment of detergents as solubility-mediating substances the respective CMC can be compared with the minimum concentration causing alterations of contractions. The CMC of Tween 80 is reported to be 10–13 mg L^{-1} (Helenius & Simons 1975; Pfüller 1986); thus solubilization occurs in a concentration range in which no significant alteration of mechanical response was observed. With a concentration of 150–190 mg L^{-1} (Helenius & Söderlund 1973; Pfüller 1986) the CMC of Triton-X 100 is much higher than the concentrations in which significant reductions were registered (0·33–3·3 mg L^{-1}). Apparently Triton-X 100 alters contractility by being incorporated into the cell membrane, whereas Tween 80 mostly appears to impede the mechanical responses by solubilization of membrane components in detergent-micelles.

Judgement of the usefulness of a solvent based on the results of this work can only be made in relation to the specific experiment. Small alterations of contractility will be negligible in qualitative studies and the EC10 values listed in Table 3 may serve as guidelines. Quantitative investigations or the study of small effects require the least possible effects of the solvent. We suggest that no more than a third of the concentration which causes a 10% alteration of contraction force should be used in such experiments. Table 4 summarizes these maximal tolerable concentrations. The values for the ileum and the vas deferens were calculated with the EC10 of the most sensitive preparation.

Of the two detergents studied only Tween 80 can be considered as a suitable solubility-mediating substance for experiments on isolated smooth muscle preparations. The bath concentrations should not exceed the CMC of 10–15 mg L^{-1}. Triton-X 100 should not be used because of the irreversible effects on the preparations at concentrations far below its CMC.

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