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Effect of Auranofin on Ion Transport by Rat Small Intestine

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Abstract—Auranofin, applied either mucosally or serosally, increased the potential difference and short-circuit current generated by stripped sheets of rat mid-intestine in a concentration-dependent manner. In-vivo auranofin induced a net fluid secretion, suggesting that the rise in electrical activity represented a stimulation of anion secretion. Removal of chloride or addition of frusemide inhibited the auranofin-induced increase in short-circuit current, indicating that chloride was the anion involved and in the case of serosal auranofin this was confirmed by direct measurement of ion fluxes. The effects of both mucosal and serosal auranofin were calcium-dependent. The gold component of the auranofin molecule is probably responsible for its secretory actions as these were mimicked by chlorauric acid. The ability of auranofin to stimulate intestinal secretion may contribute to its diarrhoeagenic action.

Auranofin ((1-thio-β-D-glucopyranosato) (triethylphosphine) gold 2,3,4,6-tetra-acetate) is an orally active and effective drug in the treatment of rheumatoid arthritis. Compared with other gold compounds used in this condition, auranofin appears to be well-tolerated, with side effects such as rash, pruritis, stomatitis and proteinuria, being less common than with parenteral gold treatment. Auranofin does however, cause disturbances of bowel function, ranging from loose stools to diarrhoea (Heuer & Morris 1983). It has been shown that auranofin inhibits the absorption of nutrients, bile acid, sodium and fluid by the small intestine (Hardcastle et al 1986a, 1987), and of fluid and sodium by the colon (Hardcastle et al 1986b). This inhibition of sodium-linked absorption may be due to the reduction in Na^+, K^+-ATPase activity induced by the drug (Fondacaro et al 1986). An inhibition of absorption is not the only factor that could contribute to an increased amount of fluid in the intestinal lumen as the volume of fluid in the gut represents a dynamic balance between absorptive and secretory processes. It is therefore necessary to consider whether auranofin affects intestinal secretory mechanisms.

Materials and Methods

Male albino rats, 230–260 g obtained from the Sheffield Field Laboratories, were allowed free access to food (diet 86, Oxoid, London) and water. They were anaesthetized with sodium pentabarbitone (60 mg kg^{-1} i.p.).

Measurement of intestinal electrical activity in-vitro

The potential difference (PD), short-circuit current (SCC) and resistance (R) were measured in-vitro across paired sheets of rat mid-intestine from which the muscle layers had been removed. Sheets (exposed area = 1·925 cm^2) were clamped between two Perspex chambers and incubated at 37°C in Krebs bicarbonate saline (Krebs & Henseleit 1932) gassed with 95% O_2/5% CO_2. The serosal solution contained 10 mM glucose and the mucosal solution 10 mM mannitol and each had a volume of 5 mL. The PD across the intestinal sheet was measured using salt bridge electrodes connected via calomel half cells to a differential input electrometer. Current was applied across the tissue through Ag/AgCl electrodes which made contact with mucosal and serosal solutions via wide bore salt bridges. When short-circuiting the tissue a correction was made for the resistance of the medium as described by Field et al (1971). Tissue resistance (R) was calculated from PD and SCC measurements using Ohm's law.

Low calcium conditions were achieved by omitting calcium from the serosal solution and adding 0·5 mM EGTA to remove interstitial calcium.

Chloride-free medium was composed by replacing chloride with sulphate and maintaining isotonicity with mannitol.

Once the tissue had been mounted it was allowed to stabilize for 10 min, after which time readings were taken at one or two min intervals. Results were expressed in one of two ways: 1. Mucosal auranofin induced a transient effect which was taken as the difference between the SCC at the peak of the response and the value immediately before the addition of the drug.

2. Serosal auranofin induced a small but sustained effect which was measured over a 55 min period. The magnitude of the response was determined by measuring the charge generated in the presence of auranofin in mC cm^{-2} (millicoulombs $cm^{-2} = \mu A\ cm^{-2} \times$ time in $s \times 10^{-3}$) and subtracting from it the baseline value measured in the period immediately before the addition of the drug.

Auranofin was dissolved in ethanol and all control sheets received an equivalent volume (2% v/v) of this vehicle. In the experiments with frusemide and verapamil, these agents were added to the test sheet as soon as it was set up. Control sheets received an equivalent volume of the vehicle (frusemide–0·5% v/v dimethylsulphoxide, DMSO; verapamil–0·8% v/v methanol) which had no significant effect on the electrical activity of the intestinal sheets ($P > 0{\cdot}05$ in all cases).

Measurement of sodium and chloride fluxes in-vitro

Sodium and chloride fluxes were measured simultaneously using the stripped intestinal sheet preparation described

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above. 0·5 μCi ^{22}Na and 1·0 μCi ^{36}Cl were added to either the mucosal or serosal solution and measurements began after 25 min, by which time steady-state fluxes had been achieved. The appearance of the tracers in the 'receiving' compartment was determined during a 10 min control period and during successive 10 min periods after the addition of auranofin. 0·5 mL samples were taken from both mucosal and serosal compartments at the beginning and end of each period, the volume removed being replaced with unlabelled solution. Samples were added to 3·5 mL Optiphase (LKB Instruments Ltd) in inserts and counted for ^{22}Na in an automatic well-type gamma counter (Packard Auto-Gamma 500), together with a ^{22}Na standard. After counting, the inserts were placed in scintillation vials and counted in a liquid scintillation counter (LKB 1215 Rackbeta). The ^{22}Na gamma counts, multiplied by a factor for the relative efficiency of the two counters for ^{22}Na, were subtracted from the total beta counts to give the ^{36}Cl counts.

The net flux was calculated as the difference between the two unidirectional fluxes measured in paired sheets of intestine taken from adjacent regions. Their resistances did not differ by more than 15%. Where appropriate, the residual ion flux was taken as the difference between the mean SCC for the two sheets and the sum of the net sodium and chloride fluxes.

Measurement of intestinal fluid transport in-vivo

Fluid transport in-vivo was assessed using a modification of the method of Robert et al (1976). A 10 cm segment of mid-intestine was cannulated and washed out with 154 mM NaCl. Any remaining fluid was gently blown out. The distal end of the segment was then tied off and approximately 0·5 mL 154 mM NaCl was added to the lumen from a syringe that was weighed before and after the addition. The proximal end was then tied and the preparation left for 15 min. At the end of this period the intestinal segment was excised from the animal and weighed before and after its contents had been drained. Fluid transport was taken as the difference between the volume of fluid added to the segment and that recovered from it at the end of the incubation. This was related to the weight of the empty loop and expressed as mL g^{-1} wet weight/15 min. A positive value indicates net absorption and a negative value net secretion of fluid.

Auranofin was administered either intraperitoneally ($1{\cdot}47 \times 10^{-5}$ mol kg^{-1}) or intraluminally ($1{\cdot}47 \times 10^{-4}$ M) with control animals receiving an equivalent volume of the vehicle (1% v/v ethanol in 154 mM NaCl) either intraperitoneally or intraluminally as appropriate.

Expression of results

Results are expressed as mean values $\pm$ 1 s.e. of the mean of the number of observations indicated. Significance was assessed using Student's t-test, paired or unpaired as appropriate.

Chemicals

Glucose was obtained from May & Baker Ltd, Dagenham; dimethylsulphoxide from BDH Chemicals Ltd, Poole; fruse-

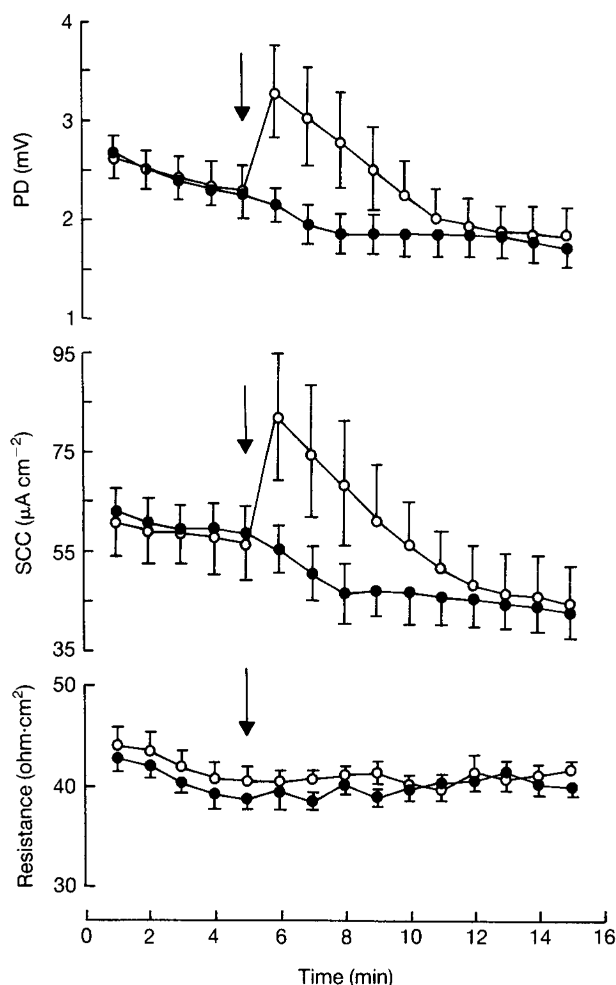

FIG. 1. Effect of mucosal auranofin on the electrical activity of stripped sheets of rat mid-intestine. At the time indicated by the arrow, auranofin ($1{\cdot}1 \times 10^{-4}$ M) was added to the test sheets (○) and an equivalent volume of the vehicle (1% ethanol) to the control sheets (●). Each point represents the mean $\pm$ 1 s.e. of the mean of 5 test and 7 control sheets.

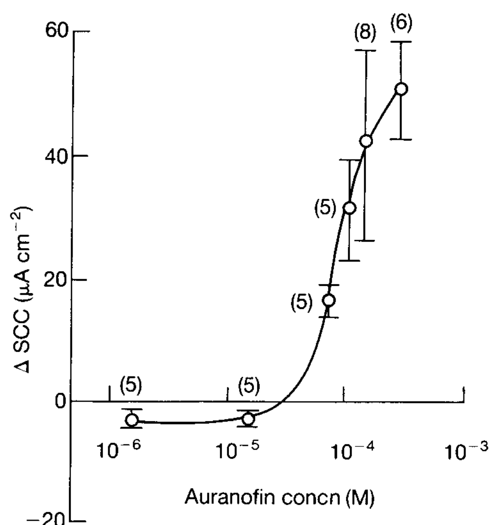

FIG. 2. Relationship between the concentration of auranofin added to the mucosal fluid and the rise in SCC (ΔSCC) generated by stripped sheets of rat mid-intestine. Each point represents the mean $\pm$ 1 s.e. of the mean of the number of observations indicated.

mide (furosemide) from Sigma Chemical Co. Ltd, Poole; verapamil from Abbot Laboratories Ltd, Queenborough, Kent; EDTA (ethylene glycol-bis-(β-amino-ethyl ether) N,N'-tetra-acetic acid) and chlorauric acid from BDH Chemicals Ltd, Poole. ^{22}Na and ^{36}Cl were supplied by Amersham International plc, Amersham, Bucks. Auranofin was a gift from Smith, Kline & French Laboratories Ltd, Welwyn Garden City, Herts.

Results

Effect of auranofin on the electrical activity of intestinal sheets

The intestinal sheets generated a PD of 2·7±0·3(7) mV, a SCC of 62·7±4·9(7) μA cm^{-2} and had a R of 42·9±1·3(7) ohm. cm^2. Mucosal addition of auranofin ($1{\cdot}1\times10^{-4}$ M) increased both the PD and SCC generated by intestinal sheets ($P<0{\cdot}001$ in both cases), without altering significantly

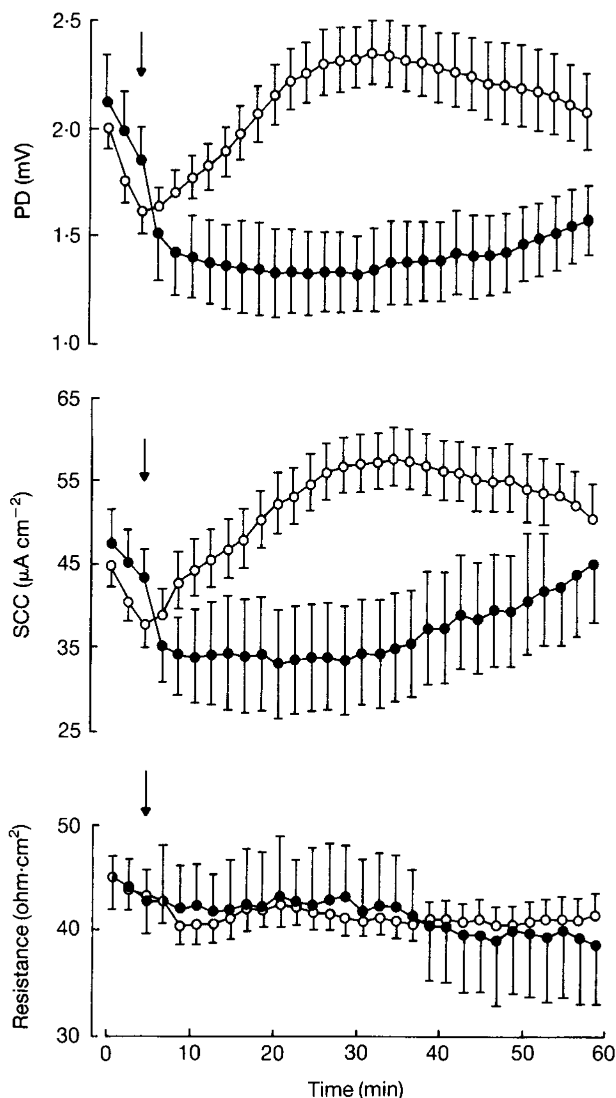

FIG. 3. Effect of serosal auranofin on the electrical activity of stripped sheets of rat mid-intestine. At the time indicated by the arrow, auranofin ($1{\cdot}1\times10^{-4}$ M) was added to the test sheets (O) and an equivalent volume of the vehicle (1% ethanol) to control sheets (●). Each point represents the mean ± 1 s.e. of the mean of 9 test and 6 control sheets.

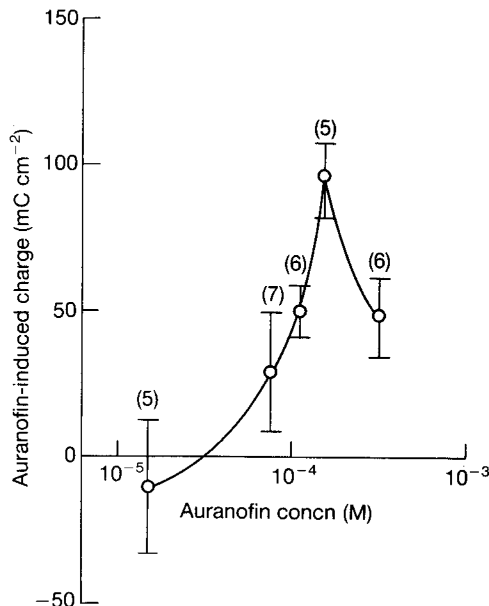

FIG. 4. Relationship between the concentration of auranofin added to the serosal fluid and the charge generated in response to the drug by stripped sheets of rat mid-intestine. Each point represents the mean ± 1 s.e. of the mean of the number of observations indicated.

($P>0{\cdot}05$) tissue R (Fig. 1). The response was transient with the maximum change in PD (1·3±0·3(5) mV) and SCC (31·4±7·6(5) μA cm^{-2}) occurring within 2 min of auranofin addition. This effect of auranofin was concentration-dependent (Fig. 2). The vehicle used, ethanol (2% v/v), produced no significant changes in PD or R ($P>0{\cdot}05$ in both cases), although there was a small decrease in SCC ($P<0{\cdot}05$).

When applied serosally, auranofin ($1{\cdot}1\times10^{-4}$ M) induced slower and more sustained rises in PD and SCC (Fig. 3). Over a 55 min period auranofin induced a mean increase in PD of 0·5±0·1(6) mV and in SCC of 15·1±2·5(6) μA cm^{-2}, without altering R ($P>0{\cdot}05$). The magnitude of the response was related to the auranofin concentration, although at the highest concentration tested ($2{\cdot}95\times10^{-4}$ M) the response was attenuated (Fig. 4). The addition of the ethanol vehicle (2% v/v) to the serosal solution had no effect on PD, SCC or R ($P>0{\cdot}05$ in all cases).

Effect of auranofin on fluid transport in-vivo

Under control conditions there was a net absorption of fluid from the intestinal loop and this was reversed by auranofin, administered either intraluminally ($1{\cdot}47\times10^{-4}$ M) or intraperitoneally ($1{\cdot}47\times10^{-5}$ mol kg^{-1}) to a net secretion (Table 1).

Effect of chloride-free serosal fluid or frusemide on the electrical responses of intestinal sheets to auranofin

The absence of chloride in the serosal fluid reduced the responses to both mucosal and serosal auranofin (Table 2). It also reduced the rise in SCC associated with sodium-linked glucose (10 mM in mucosal fluid) absorption from 123·4±13·0(7) to 87·4±2·2(7) μA cm^{-2} ($P<0{\cdot}01$). This degree of inhibition was however, significantly less than that observed with either mucosal ($P<0{\cdot}001$) or serosal ($P<0{\cdot}01$) auranofin, suggesting that non-specific effects of

lack of serosal chloride could not entirely account for the reduction in the responses to auranofin.

Frusemide reduced the responses to both mucosally and serosally applied auranofin (Table 2), without altering the effect of mucosal glucose ($P > 0{\cdot}05$).

Involvement of calcium in the electrical responses of intestinal sheets to auranofin

Removal of serosal calcium reduced the response to both mucosal and serosal application of auranofin (Table 3). A similar effect was observed in the presence of the calcium channel blocker, verapamil, in the serosal fluid (Table 3). Neither of these conditions affected the rise in SCC induced by the addition of 10 mM glucose to the mucosal fluid ($P > 0{\cdot}05$ in both cases), indicating that they had not caused non-specific tissue damage (control = $120{\cdot}0 \pm 4{\cdot}9(5)$, calcium-free = $111{\cdot}3 \pm 11{\cdot}1(5)$ μA cm^{-2}; control = $127{\cdot}6 \pm 11{\cdot}3(7)$, +verapamil = $110{\cdot}7 \pm 11{\cdot}3(7)$ μA cm^{-2}).

Effect of auranofin on sodium and chloride fluxes in intestinal sheets

The effect of mucosal auranofin was transient and no changes in ion fluxes could be detected upon its addition. Serosal auranofin however, induced a sustained rise in SCC and this was associated with an increase in serosal to mucosal chloride movement which, since the mucosal to serosal

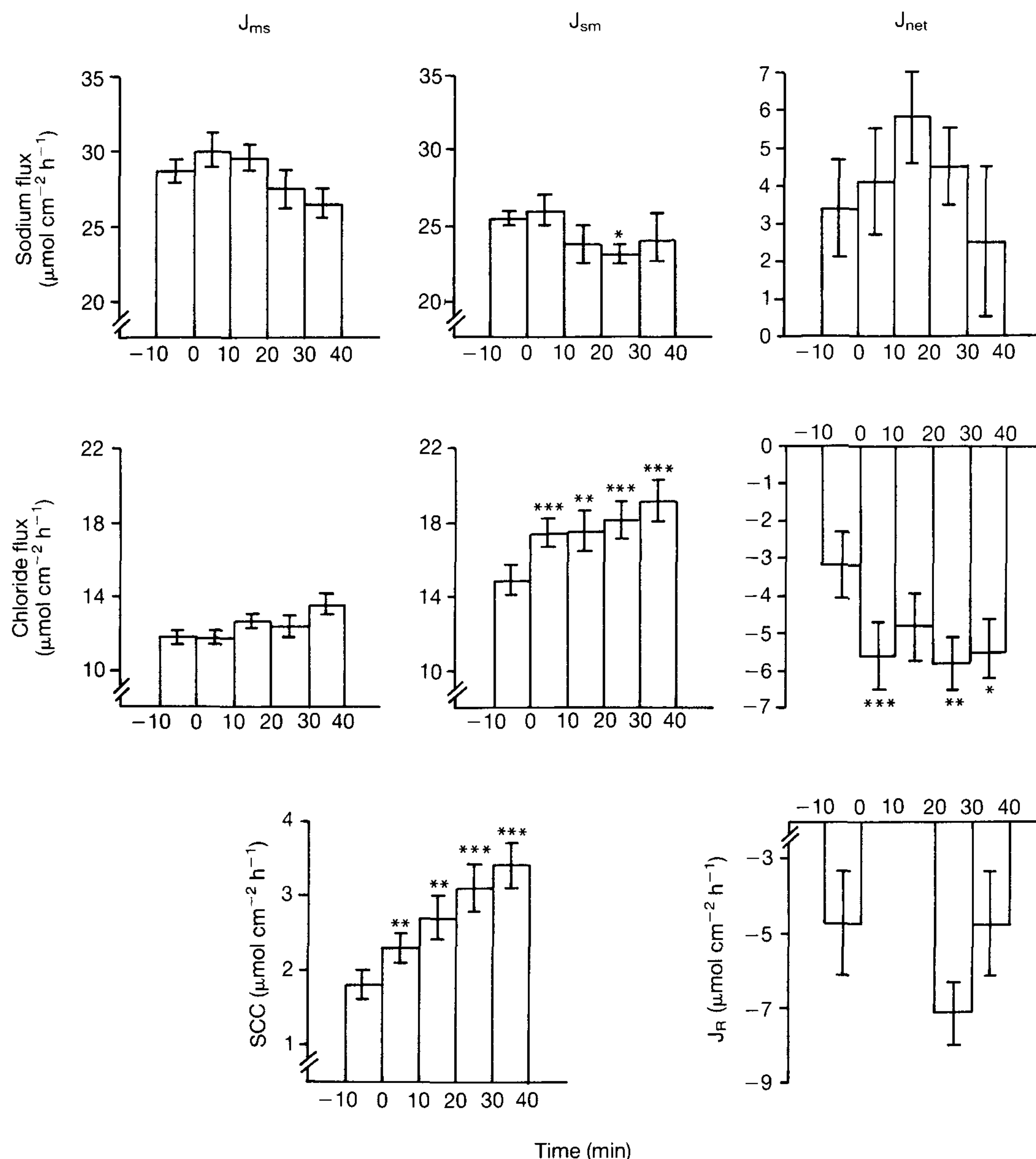

FIG. 5. Effect of serosal auranofin ($1{\cdot}1 \times 10^{-4}$ M) on sodium and chloride fluxes and the mean SCC across stripped sheets of rat mid-intestine. The mucosal-to-serosal (J_{ms}) and serosal-to-mucosal (J_{sm}) fluxes were measured in adjacent segments of tissue and the net flux (J_{net}) determined as the difference between the two unidirectional fluxes. The residual ion flux (J_R) was calculated as the difference between the mean SCC and the sum of net sodium and chloride fluxes. Each bar represents the mean ± 1 s.e. of the mean of 7 observations with a paired *t*-test being used to assess the significance of auranofin action (* = $P < 0{\cdot}05$, ** = $P < 0{\cdot}01$, *** = $P < 0{\cdot}001$).

Table 1. Effect of auranofin on fluid transport across rat mid-intestine in-vivo. When applied intraluminally (i.l.), auranofin was present in the intestinal loop at a concentration of $1·47 \times 10^{-4}$ M, with control animals being exposed to an equivalent concentration of vehicle (1% ethanol). When administered intraperitoneally (i.p.), auranofin was added to the peritoneal fluid at a dose of $1·47 \times 10^{-5}$ mol kg^{-1}, with control animals receiving an equivalent volume of vehicle (0·5 mL 1% ethanol). Each value represents the mean ± 1 s.e. of the mean of the number of observations in parentheses. A positive value indicates net absorption and a negative value net secretion. An unpaired *t*-test was used to assess the significance of auranofin action.

	Fluid transport (mL g^{-1} wet wt/15 min)		
	Control	Test	*P*
Auranofin i.l.	0·18±0·04(4)	−0·14±0·05(4)	<0·01
Auranofin i.p.	0·14±0·09(4)	−0·28±0·09(4)	<0·01

Table 2. Effect of chloride-free conditions or frusemide on the SCC response of stripped sheets of rat mid-intestine to mucosal (M) or serosal (S) auranofin ($1·1 \times 10^{-4}$ M). Chloride in both M and S solutions was replaced with sulphate and isotonicity maintained with mannitol. Frusemide (10^{-3} M) was present in the S solution with an equivalent volume of vehicle (0·5% DMSO) added to control sheets. Each point represents the mean ± 1 s.e. of the mean of the number of observations in parentheses and the significance of the difference between control and test sheets was determined by a paired *t*-test.

	Auranofin M (μA cm^{-2})	Auranofin S (mC cm^{-2})
Control	45·9±13·2(6)	129·2±12·2(6)
Chloride-free	0·4±2·7(6)	42·5±10·2(6)
	P<0·05	*P*<0·01
Control	74·2±7·9(8)	102·5±9·8(6)
Frusemide	54·0±7·3(8)	7·9±6·2(6)
	P<0·01	*P*<0·001

movement of this ion was unchanged, resulted in an enhanced net secretion of chloride in each of the four 10 min periods following its addition (Fig. 5). Serosal auranofin had little effect on either sodium fluxes or the residual ion flux (Fig. 5).

Effect of chlorauric acid on the electrical activity of intestinal sheets

Chlorauric acid ($1·1 \times 10^{-4}$ M) induced similar changes in electrical activity to those observed with the same concentration of auranofin. When added to the mucosal fluid,

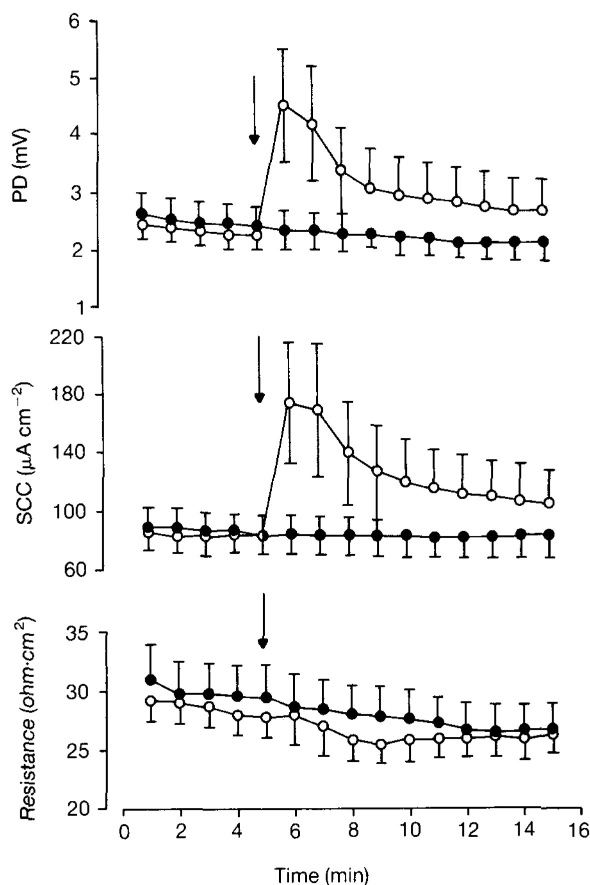

FIG. 6. Effect of mucosal chlorauric acid on the electrical activity of stripped sheets of rat mid-intestine. At the time indicated by the arrow, chlorauric acid ($1·1 \times 10^{-4}$ M) was added to test sheets (○) and an equivalent volume of vehicle (1% ethanol) was added to control sheets (●). Each point represents the mean ± 1 s.e. of the mean of 6 test and 6 control sheets.

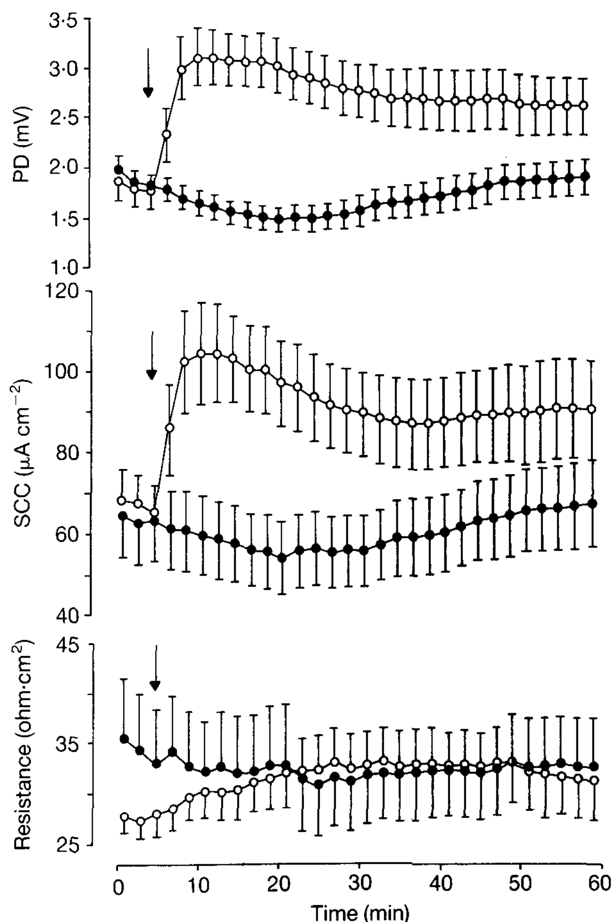

FIG. 7. Effect of serosal chlorauric acid on the electrical activity of stripped sheets of rat mid-intestine. At the point indicated by the arrow, chlorauric acid was added to test sheets (○) and an equivalent volume of vehicle (1% ethanol) to control sheets (●). Each point represents the mean ± 1 s.e. of the mean of 7 test and 7 control sheets.

Table 3. Involvement of calcium in the SCC response of stripped sheets of rat mid-intestine to mucosal (M) or serosal (S) auranofin ($1 \cdot 1 \times 10^{-4}$ M). Calcium-free conditions were achieved by omitting calcium from the S fluid and adding 0·5 mM EGTA. Verapamil was present at a concentration of 10^{-3} M in the S solution and control sheets received an equivalent volume of vehicle (0·8% methanol). Each point represents the mean ± 1 s.e. of the mean of the number of observations in parentheses and the significance of the difference between control and test sheets was determined by a paired t-test.

	Auranofin M (μA cm^{-2})	Auranofin S (mC cm^{-2})
Control	48·9 ± 12·2(6)	82·9 ± 8·6(6)
Calcium-free	4·0 ± 1·5(6)	−10·6 ± 4·7(6)
	$P<0 \cdot 05$	$P<0 \cdot 001$
Control	22·9 ± 4·0(6)	77·6 ± 5·9(8)
Verapamil	5·3 ± 3·2(6)	31·0 ± 10·4(8)
	$P<0 \cdot 05$	$P<0 \cdot 05$

chlorauric acid caused a transient rise in PD and SCC, with maximum changes of 2·3 ± 0·9(6) mV and 94·2 ± 35·6(6) μA cm^{-2}, respectively (Fig. 6), while serosal application induced a sustained increase in PD (mean increase = 1·1 ± 0·1(7) mV) and SCC (mean increase = 27·5 ± 5·5(7) μA cm^{-2}) (Fig. 7). In neither case was there a change in R ($P>0 \cdot 05$).

Discussion

Auranofin has been shown previously to inhibit the sodium-dependent absorption of nutrients in the small intestine (Fondacaro et al 1986; Hardcastle et al 1986a, 1987), an effect that will lead to a reduced movement of fluid from the gut lumen and a tendency to loose stools. The present study indicates that this problem may be exacerbated by the ability of auranofin to induce a secretory response in the small intestine.

Both mucosal and serosal application of auranofin to intestinal sheets increased the SCC (Figs 1–4), a reflection of net electrogenic ion transport. Such an effect could result from a stimulation of either cation absorption or anion secretion. In-vivo experiments showed that auranofin, administered either intraluminally or intravenously, reversed the direction of net fluid movement across intestinal loops from absorption to secretion (Table 1), suggesting that the increased SCC observed in-vitro was due to a stimulation of anion secretion. The principal ion involved appears to be chloride since the response to both mucosal and serosal auranofin was reduced by removal of chloride ions from the bathing solution or by the presence of serosal frusemide (Table 2), an agent that inhibits the uptake of chloride at the basolateral border of the enterocyte (Frizzell et al 1979). In the case of serosal auranofin the stimulation of chloride secretion was confirmed in experiments where sodium and chloride fluxes were measured directly (Fig. 5). Chloride movement from serosa to mucosa was enhanced, leading to an increase in net chloride secretion. Sodium fluxes and the residual ion flux were unaltered so that the increased chloride secretion entirely accounted for the rise in SCC. It was not possible to determine the effects of auranofin on ion fluxes when it was applied to the mucosal side of the tissue, since it produced a transient response so that steady-state conditions would not prevail. However, the ion replacement experiments and the effects of frusemide (Table 2) suggest that auranofin also induces a net secretion of chloride ions when it is applied to the mucosal side of the tissue.

The failure of serosal auranofin to alter sodium fluxes contrasts with an earlier report in which auranofin was shown to inhibit the absorption of this ion (Hardcastle et al 1986a). This may arise from differences in both the site of auranofin application and the intestinal preparation used. Flux determinations were performed using a stripped intestinal sheet with auranofin present on the serosal side, while in the previous study auranofin was added to the mucosal solution of an everted sac.

The chloride secretory mechanism requires the uptake of chloride against its electrochemical gradient across the basolateral membrane, energy being provided by the sodium gradient which is maintained by the sodium pump. It may seem inconsistent that an agent that inhibits the sodium pump should also activate the secretory process, but it has been reported recently that ouabain, which also inhibits the sodium pump, stimulates chloride secretion by the isolated ileal mucosa of the rabbit (Hubel & Renquist 1988). This effect was attributed to the actions of oubain on the sodium pump of the enteric neurons leading to a depolarization and the release of secretory neurotransmitters. Auranofin may act similarly.

The effects of both mucosal and serosal auranofin were dependent upon calcium, being reduced in the absence of serosal calcium or in the presence of the calcium channel blocker, verapamil (Table 3). The activation of secretion at the enterocyte (Donowitz 1983) and the release of neurotransmitters (Haynes & Murad 1980) both require calcium, but the data in Table 3 do not distinguish between an action of auranofin on the enterocyte or on the enteric neurons, although these experiments were carried out on stripped intestinal sheets where the enteric nervous system is incomplete.

Auranofin has been shown recently to cause the translocation of protein kinase C from cytosol to the particulate subcellular fraction (Zalewski et al 1988). Since this enzyme is thought to be involved in the activation of intestinal secretion (Chang et al 1985; Fondacaro & Henderson 1985) such an action of auranofin may contribute to its ability to promote intestinal secretion.

The gold component of the auranofin molecule may be responsible for its secretory actions since chlorauric acid produced similar effects (Figs 6, 7). The mechanism by which gold produces these effects is not yet clear.

Two actions of auranofin may now be considered to contribute to its diarrhoeagenic action—firstly its ability to inhibit sodium-linked absorption and secondly its stimulatory actions on the intestinal secretory mechanism. Both of these effects will enhance the volume of fluid retained in the intestinal lumen and this may be responsible, at least in part, for the increased tendency to loose stools that is experienced by patients taking the drug.

Acknowledgement

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