Table 1 Inhibition by dopamine of nerve mediated constriction of rat mesenteric artery and effects of haloperidol and yohimbine. The magnitude of the effect is expressed as percentage reductions (± s.d.) of the control responses

		Haloperidol		*Yohimbine*
	Control	*0.1 μM*	*0.5 μM*	*10 μM*
Dopamine	*(n-12)*	*(n-6)*	*(n-5)*	*(n-6)*
0.1 μM	17.5 ± 3.6	5.2 ± 3.2	0	—
0.5 μM	31.3 ± 4.7	8.2 ± 2.6	2.8 ± 1.4	29.6 ± 2.7
1 μM	46.6 ± 3.9	11.7 ± 2.8	4.5 ± 1.6	41.9 ± 3.6

al., 1978) or mediated through a prejunctional α-adrenoceptor (Hurst, Marshall & Nasmyth, 1979). We have investigated the effects of dopamine on the vasoconstrictor responses in the perfused rat mesenteric artery preparation (McGregor, 1965). The perfusion fluid contained cocaine (100 μM) and the periarterial nerves were stimulated for 30 s, every 5 min (10 or 20 Hz; 1 ms; 20 V). Doses of noradrenaline (0.1 to 20 μg) were injected into the perfusion.

Infusion of dopamine (0.1–1 μM) resulted in immediate depression of the vasoconstrictor responses to nerve stimulation (Table 1). The results with concentrations of dopamine higher than 1 μM are not included because they inhibited the responses to exogenous noradrenaline, suggesting an additional postsynaptic effect. This inhibition was slow in onset and difficult to wash off.

The dopamine receptor antagonist haloperidol, in concentrations (0.1–0.5 μM) that had no effect on responses to nerve stimulation or to noradrenaline, reduced the depressant effect of dopamine on neuronally mediated vasoconstriction (Table 1).

Yohimbine (10 μM) produced a 10 to 15% increase in the response to nerve stimulation, but did not alter the inhibitory effect of dopamine (Table 1).

It is suggested that dopamine inhibition of vasoconstrictor responses to nerve stimulation in rat mesentric artery may be mediated by a specific inhibitory dopamine receptor and not via presynaptic α-adrenoceptors.

The mechanism of the slow dopamine inhibition of noradrenaline responses has not yet been defined.

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The influence of old age and of renal failure on hepatic glucuronidation in the rat

M. ALI, P.J. NICHOLLS & A. YOOSUF

Welsh School of Pharmacy, UWIST, Cardiff CF1 3NU, U.K.

There is evidence that the metabolism of some drugs may be altered in old age (Crooks, O'Malley & Stevenson, 1976) and in patients with renal failure (Reidenberg, 1975). The present investigation has examined whether these factors affect glucuronide conjugation in rat liver.

The animals were laboratory bred male Wistar rats of 8 and 30 months age (mean body weights 272 and 549 g respectively). Renal failure was induced by either sub-total nephrectomy (McCance & Morrison, 1956) or ligation of both renal pedicles under halothane anaesthesia. The control animals for the nephrectomized rats were sham-operated and pair-fed. The *in vitro* glucuronidation of 4-nitrophenol and

of phenolphthalein was determined by procedures described by Storey (1964) and Dutton (1966) respectively, using the 2000 *g* supernatant of 10% (w/v) rat liver homogenates in 0.25 M sucrose. Microsomal protein was determined on the fraction of the liver homogenates sedimenting between 10,000 and 100,000 *g*.

There were significant ($P < 0.05$) decreases in liver to body weight ratios, mg total protein g^{-1} liver, and mg microsomal protein g^{-1} liver in the 30-month-old control rats compared with 8-month-old control animals. The rates of conjugation of both substrates were also significantly ($P < 0.05$) lowered to a small extent in the older rats: rates (n mole substrate conjugated mg^{-1} microsomal protein min^{-1}; means ± s.e. of 5 rats) for 8- and 30-month-old animals respectively, were 4.6 ± 0.1 and 3.5 ± 0.1 for 4-nitrophenol (at a substrate concentration of 2 mM) and 11.9 ± 0.2 and 10.8 ± 0.1 for phenolphthalein (at a substrate concentration of 0.2 mM). The Km values for both substrates were unaltered by old age with respect to glucuronidation.

Nephrectomy had no significant effect on the rate of conjugation of 4-nitrophenol by liver from both 8- and 30-month-old rats. However, the rate of glucuronidation of phenolphthalein was significantly ($P < 0.05$) reduced to a small extent 1 day after total and 14 and 35 days after sub-total nephrectomy in the rats of both age groups, e.g. at a substrate concentration of 0.2 mM, the rate of conjugation (n mole phenolphthalein conjugated mg^{-1} microsomal protein min^{-1}; means ± s.e. of 5 rats) was 12.0 ± 0.5 (controls) and 8.9 ± 0.4 (nephrectomized) in 8-month-old rats, 14 days after sham-operation or nephrectomy. The Km value for phenolphthalein in this system was unaltered by nephrectomy.

If decreases of a similar magnitude occur in the hepatic glucuronidation pathway in old age and renal failure in man, it is unlikely that they would be of great clinical importance.

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Studies on a cell-mediated immune response in the guinea-pig colon

A.J. LEWIS, A.A. NORRIS & I.J. ZEITLIN

Department of Physiology and Pharmacology, University of Strathclyde, Glasgow, and Organon Laboratories Limited, Newhouse, Lanarkshire.

The guinea-pig colon has been shown to participate in delayed-type hypersensitivity reactions (Rosenberg & Fischer, 1964), using the contact allergen, 2,4-dinitro-1-chlorobenzene, (DNCB) for cutaneous sensitization and intrarectal challenge. This model has subsequently been proposed for the investigation of the pathogenesis of inflammatory bowel disease by several workers (Bicks & Rosenberg, 1964; Askenase, Boone & Binder, 1978).

We have examined the effects of varying the sensitization and challenge regimens using DNCB, in an attempt to establish such a model with a view to making it a potential screening system for studying the action of anticolitic drugs and other therapeutic agents.

Male, Dunkin Hartley guinea-pigs (170–200 g) were used in all experiments. Several groups were sensitized on the shaved skin of the neck to 50 µl of 2.5% DNCB in ethanol for three consecutive days. After an interval of seven days the animals were challenged intrarectally using 0.25% DNCB in Orabase (E.R. Squibb Ltd.) for five successive days. Confirmation of systemic sensitization was achieved the day prior to intrarectal challenge by skin testing on the ear and measuring the increased skin thickness after 24 hours. Fifty µl of 0.25% DNCB in ethanol produced a 36% ± 9% increase in skin thickness. Macroscopically, the most intense inflammatory response in the colon was observed 24 h after the final challenge and showed erythema and fine punctate lesions. Histologically the lesion was characterized by increased cellular infiltration, including macrophages, plasma cells