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ANTAGONISM OF VASODEPRESSOR AND GASTRIC SECRETORY RESPONSES TO HISTAMINE BY THE H_2-RECEPTOR ANTAGONISTS, RANITIDINE AND CIMETIDINE, IN THE ANAESTHETIZED DOG

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1 The new H_2-receptor antagonist, ranitidine, has been compared with cimetidine as an inhibitor of gastric acid secretion in the anaesthetized dog.

2 Both ranitidine and cimetidine given intravenously inhibited histamine-induced gastric secretion in a dose-related manner. Ranitidine was 4.2 times more potent than cimetidine when given as an intravenous infusion and 9.6 times more potent as an intravenous bolus dose.

3 In a separate series of experiments, ranitidine was compared with cimetidine as an antagonist of vasodepressor responses to histamine. Mepyramine alone displaced the histamine dose-response curve to the right. After a maximally effective dose of mepyramine, further displacement could be achieved with ranitidine and cimetidine, ranitidine being 19.2 times more potent than cimetidine.

4 Ranitidine alone had no effect on vasodepressor response curves to histamine, acetylcholine or (−)-isoprenaline or on vasopressor response curves to phenylephrine.

5 These results indicate that displacement of the histamine dose-response curve after mepyramine blockade by ranitidine and cimetidine is due to selective H_2-receptor antagonism.

Introduction

We have previously shown that the H_2-receptor antagonist, ranitidine (AH 19065), is a potent inhibitor of gastric secretion in the anaesthetized rat (Daly, Humphray & Stables, 1980b) and the conscious dog with a Heidenhain pouch (Daly, Humphray & Stables, 1980a) or with a gastric fistula (Daly, Humphray & Stables, 1979a). We have now investigated the antisecretory and cardiovascular effects of ranitidine and cimetidine in the anaesthetized dog.

There have been only a few reports of the use of the anaesthetized dog with an acute gastric fistula for the assessment of gastric acid secretion (Black, Fisher & Smith, 1958; Curwain & Holton, 1973). This preparation has the advantage of allowing simultaneous measurement of gastric secretion, cardiovascular and respiratory parameters. Also pylorus ligation eliminates contamination of the gastric juice resulting from duodenal reflux and loss of gastric juice as a result of stomach emptying.

The cardiovascular response to histamine has been shown to be mediated via both H_1- and H_2-receptors. Black, Owen & Parsons (1975) have shown that after maximal displacement of the histamine depressor dose-response curve by mepyramine, further displacement can be achieved with metiamide. In a series of experiments we have compared the actions of ranitidine with those of cimetidine on the vascular responses to histamine and other vasoactive substances in the anaesthetized dog. A preliminary account of some of these findings has been given to the British Pharmacological Society (Daly, Humphray & Stables, 1979b).

Methods

Beagle dogs of either sex weighing 6 to 14 kg were deprived of food overnight and anaesthetized with thiopentone (25 mg/kg i.v.) followed by chloralose (50 mg/kg i.v.) and urethane (500 mg/kg i.v.). Supplementary doses of chloralose and urethane were given as necessary to maintain anaesthesia. The trachea was intubated with a cuffed endotracheal tube. A femoral artery was cannulated to allow measurement of systemic blood pressure with a Hewlett Packard 1280 blood pressure transducer. A Hewlett Packard 7754A recorder was used to monitor blood pressure, heart rate (which was automatically derived from the blood pressure), and intrathoracic pressure changes. Intrathoracic pressure changes were measured from a

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slightly inflated balloon in the oesophagus connected to a Hewlett Packard 1280 pressure transducer.

Intravenous bolus doses of drugs or anaesthetic were administered via a cannula inserted into a femoral vein. Intravenous infusions of drugs were administered via a catheter inserted into a brachial vein.

Gastric antisecretory study

The dog was prepared for collection of gastric secretion from the whole stomach as follows: the stomach was exposed by laparotomy and a double purse string suture inserted in the most dependent portion of the stomach. A Gregory duodenal cannula was then inserted through a small incision in the stomach wall and firmly secured by the purse string sutures. The pylorus was ligated and the Gregory cannula anchored to the body wall by sutures. The incisions in the body wall and skin were closed around the barrel of the Gregory cannula with sutures or clips. The dog was then laid on its side and the stomach washed clean with water at body temperature, poured through a tube which had been passed down the oesophagus into the stomach. The dog was then placed prone in a hammock with a central hole for the Gregory cannula, and the hammock raised until the dog was in a standing position. A teflon insert was passed up the fistula to lift the dorsal stomach wall from the opening of the fistula and allow drainage of any gastric secretion. A plastic collection vessel was attached to the end of the cannula and changed, either every 10 or 15 min. Collections of basal secretion were made for at least 30 min and then gastric secretion was stimulated by an intravenous infusion of histamine (1 $\mu g\ kg^{-1}\ min^{-1}$) via a fine catheter inserted into a brachial vein. The volume of gastric secretion was measured either every 10 or 15 min and H^+ concentration measured by titrating an aliquot to pH 7 against 0.1 M NaOH using a Radiometer TTT2 autotitrator. Acid output was then calculated in $\mu mol\ H^+$ per min. Once a plateau of gastric acid secretion had been obtained, ranitidine or cimetidine was administered intravenously either as a bolus dose or as an infusion for 30 min in saline at the rate of 1 ml/min.

Ranitidine was administered intravenously in bolus doses of 0.01 to 0.10 mg/kg or in 30 min infusions of 1 to 10 $\mu g\ kg^{-1}\ min^{-1}$. Cimetidine was administered intravenously in bolus doses of 0.1 to 1.0 mg/kg or as infusions of 3 to 30 $\mu g\ kg^{-1}\ min^{-1}$ for 30 min. Measurements of cardiovascular and respiratory parameters were made each time the gastric collection vessel was changed.

Changes in gastric acid secretion, heart rate, blood pressure and respiratory pressure changes were calculated by comparing the mean of the 2 consecutive values at peak drug response with the mean of the 4 control values preceding the drug. Gastric acid secretion and respiratory pressure changes were calculated as % change, whereas heart rate changes were expressed in beats/min and blood pressure changes in mmHg.

Blood pressure study

Dose-response curves for falls in diastolic blood pressure were made by intravenous injection of histamine 0.03 to 3 μg/kg. Control curves were repeated until constant and then mepyramine was injected in an intravenous bolus dose of 0.7 mg/kg at time zero. At +10 min the histamine dose-response curve was repeated. Ranitidine or cimetidine was then infused intravenously at a rate of 1 ml/min for 15 min before and during a further histamine dose-response curve. Ranitidine was given in doses of 1 to 300 $\mu g\ kg^{-1}\ min^{-1}$ and cimetidine in doses of 10 to 1000 $\mu g\ kg^{-1}\ min^{-1}$. Additional injections of mepyramine (0.7 mg/kg i.v.) were given 10 min before each histamine dose-response curve as preliminary experiments showed that the effects of a single dose of mepyramine were not maintained for the duration of the experiment.

In a separate series of experiments dose-response curves for falls in diastolic blood pressure were constructed by intravenous injections of histamine 0.03 to 3 μg/kg, acetylcholine 0.003 to 3 μg/kg or (−)-isoprenaline 0.003 to 1 μg/kg. Dose-response curves were also constructed to phenylephrine 0.3 to 10 μg/kg for increases in diastolic blood pressure. Control dose-response curves were repeated until constant and then ranitidine was infused at a rate of 30, 100 or 300 $\mu g\ kg^{-1}\ min^{-1}$ for 15 min before and during a further agonistdose-response curve. At the end of each experiment a known antagonist was tested as an intravenous bolus dose. Mepyramine (0.7 mg/kg) was tested against histamine, atropine (10 μg/kg) against acetylcholine, propranolol (1 mg/kg) against (−)-isoprenaline and phentolamine (1 mg/kg) against phenylephrine. The shifts in the agonist dose-response curves were expressed as dose-ratios by comparing the dose of histamine, acetylcholine or (−)-isoprenaline which gave a decrease in diastolic blood pressure of 40 mmHg before and after each antagonist. Preliminary experiments showed that this fall in blood pressure represented approximately 50% of the maximum response to these agonists. The value for phenylephrine was the dose which gave an increase in diastolic blood pressure of 25 mmHg.

Drugs

The drugs used were O-acetylcholine chloride (BDH); atropine sulphate (BDH); cimetidine (SK & F Ltd); histamine acid phosphate (BDH); (−)-isoprenaline

bitartrate dihydrate (Ward Blenkinsop & Co); mepyramine maleate (M & B); phentolamine methanesulphonate (Ciba); L-phenylephrine hydrochloride (Koch-Light); (±)-propranolol hydrochloride (ICI) and ranitidine hydrochloride (Glaxo Group Research Ltd). Drug doses are expressed as base. All drugs were dissolved in 0.9% w/v NaCl solution (saline) and solutions of (−)-isoprenaline contained ascorbic acid 20 μg/ml. The sample of propranolol was a generous gift from Dr J. Conway, ICI Ltd.

Results

Gastric antisecretory study

Intravenous bolus doses of ranitidine and cimetidine produced dose-related inhibitions of gastric acid secretion induced by histamine. Table 1 summarizes the mean inhibition of acid secretion following ranitidine and cimetidine. Regression lines have been calculated from the data used for Table 1 and ED_{50} values calculated. The ED_{50} values in mg/kg (95% confidence limits) were 0.027 (0.010–0.049) for ranitidine and 0.26 (0.18–0.38) for cimetidine. Therefore ranitidine was 9.6 times more active than cimetidine when given as an intravenous bolus dose as an antagonist of histamine-induced gastric secretion. Table 1 also shows the effects of intravenous bolus doses of ranitidine and cimetidine on heart rate, blood pressure and respiratory intrathoracic pressure changes. It can be seen that neither drug caused any appreciable change in heart rate, blood pressure or respiratory pressure at doses up to 35 to 40 times greater than their respective antisecretory ED_{50} values.

Gastric secretion was also inhibited in a dose-related manner following intravenous infusion for 30 min of ranitidine and cimetidine as shown in Table 2. The ED_{50} values in μg kg^{-1} min^{-1} (95% confidence limits) were 2.2 (1.1–3.3) for ranitidine and 9.2 (6.1 to 13.7) for cimetidine. Therefore ranitidine was 4.2 times more active than cimetidine, when given as an intravenous infusion, as an antagonist of histamine-induced gastric secretion. Table 2 shows that neither ranitidine nor cimetidine have any marked effects on blood pressure, heart rate, or respiratory pressure at any of the dose levels tested.

Blood pressure study

Histamine caused dose-dependent falls in systemic blood pressure with a threshold dose of 0.03 μg/kg (see Figures 1 and 2). The maximum dose of histamine was 3 μg/kg which gave a fall in diastolic blood pressure of 65 to 85 mmHg. No attempt was made to obtain maximal depressor responses as the blood pressure did not always return to the pre-injection level after doses in excess of 3 μg/kg. A linear dose-response relationship was obtained over the dose-range 0.1 to 3 μg/kg as shown in Figures 1 and 2. Administration of mepyramine (0.7 mg/kg i.v.) caused a parallel displacement to the right of the histamine dose-response curve with a dose-ratio of 6.95 (5.27 to 9.17, 95% confidence limits). Initial studies showed that the effects of a single dose of mepyramine

Table 1 Effects of intravenous bolus doses of ranitidine and cimetidine on gastric acid secretion, blood pressure, heart rate and intrathoracic pressure in the anaesthetized dog

Drug	*Dose* (mg/kg i.v.)	*% reduction in gastric acid secretion*	*Blood pressure change* (mmHg) *Systolic*	*Diastolic*	*Heart rate change* (beats/min)	*% Change in intrathoracic pressure*
Ranitidine	0.01	33.0 (2)	−1.5 (2)	+1.0 (2)	+2.5 (2)	0 (2)
	0.03	49.1 ± 5.7 (3)	+2.7 ± 1.5 (3)	+1.5 ± 2.6 (3)	−2.2 ± 2.2 (3)	+4.8 ± 2.7 (3)
	0.10	77.9 ± 9.6 (3)	−4.2 ± 3.1 (3)	+0.7 ± 1.3 (3)	−1.2 ± 3.9 (3)	+4.8 ± 1.3 (3)
	1.00	NR	+6.0 ± 4.9 (3)	−12.3 ± 12.7 (3)	+12.5 ± 16.6 (3)	+7.8 ± 7.8 (3)
Cimetidine	0.10	22.3 ± 3.9 (4)	−5.0 ± 2.0 (4)	−1.3 ± 0.8 (4)	−3.8 ± 1.5 (4)	+7.8 ± 5.4 (4)
	0.30	56.6 ± 10.6 (4)	−1.0 ± 2.3 (4)	+0.8 ± 0.8 (4)	−5.5 ± 2.9 (4)	+4.8 ± 2.9 (4)
	1.00	83.6 ± 1.4 (3)	−5.0 ± 5.0 (3)	−3.0 ± 3.1 (3)	−4.0 ± 4.6 (3)	−10.0 ± 10.7 (3)
	10.00	NR	−6.8 ± 9.1 (4)	−8.5 ± 7.4 (4)	−12.3 ± 12.4 (4)	−4.0 ± 3.4 (4)

Mean values ± s.e. mean are given; Figures in parentheses = number of results; NR = Not recorded

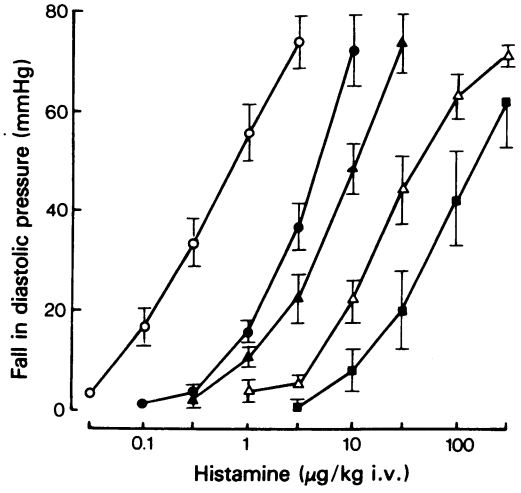

Figure 1 Vasodepressor responses in the dog to histamine alone (○) and in the presence of mepyramine 0.7 mg/kg i.v. (●), ranitidine 1 μg kg^{-1} min^{-1} i.v. (▲), ranitidine 10 μg kg^{-1} min^{-1} i.v. (△) and ranitidine 100 μg kg^{-1} min^{-1} i.v. (■).

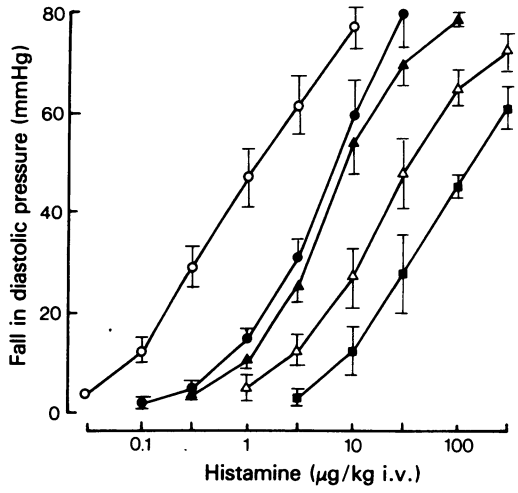

Figure 2 Vasodepressor responses in the dog to histamine alone (○) and in the presence of mepyramine 0.7 mg/kg i.v. (●), cimetidine 10 μg kg^{-1} min^{-1} i.v. (▲), cimetidine 100 μg kg^{-1} min^{-1} i.v. (△) and cimetidine 1000 μg kg^{-1} min^{-1} (■).

declined during the experiments. Therefore it was necessary to repeat injections of mepyramine (0.7 mg/kg) before each infusion of H_2-antagonist. As the H_2-antagonist was infused at up to three dose levels in each experiment, control experiments were carried out in which four successive histamine dose-response curves were constructed, each one preceded by a dose of mepyramine alone. Repeating the mepyramine doses in this way caused no further displacement of the histamine dose-response curves beyond that achieved by the first dose of mepyramine. However, intravenous infusion of ranitidine or cimetidine caused further dose-dependent parallel displacement of the histamine dose-response curve to the right (Figures 1 and 2). The dose of ranitidine which caused a five fold shift in the post-mepyramine histamine dose-response curve was 5.6 μg kg^{-1} min^{-1} compared with 110 μg kg^{-1} min^{-1} for cimetidine as shown in Figure 3. Figure 3 includes results from curves omitted from Figures 1 and 2 for clarity.

Table 2 Effects of intravenous infusion of ranitidine and cimetidine on gastric acid secretion, blood pressure, heart rate and intrathoracic pressure in the anaesthetized dog

Drug	*Dose* (μg kg^{-1} min^{-1} 30 min i.v.)	*% reduction in gastric acid secretion*	*Blood pressure change* (mmHg) *Systolic*	*Diastolic*	*Heart rate change* (beats/min)	*% change in intrathoracic pressure*
Ranitidine	1	15.7 ± 7.9 (3)	+11.5 ± 4.3 (3)	+4.0 ± 0.8 (3)	+6.5 ± 8.3 (3)	−3.2 ± 1.7 (3)
	3	82.7 ± 11.8 (3)	−1.7 ± 12.9 (3)	+7.5 ± 3.8 (3)	+4.2 ± 12.6 (3)	−2.0 (2)
	10	94.6 ± 3.3 (4)	+1.9 ± 6.2 (4)	+5.5 ± 4.4 (4)	−3.1 ± 3.2 (4)	+2.3 ± 1.7 (4)
Cimetidine	3	12.1 ± 9.5 (3)	+13.0 ± 6.6 (3)	−4.7 ± 6.8 (3)	−8.3 ± 4.4 (3)	+7.0 ± 11.3 (3)
	10	58.1 ± 10.5 (3)	+9.0 ± 2.1 (3)	0.0 ± 5.8 (3)	+6.7 ± 2.0 (3)	+3.0 ± 11.0 (3)
	30	83.2 ± 5.1 (3)	+5.0 ± 5.8 (3)	−2.3 ± 6.4 (3)	+8.3 ± 6.0 (3)	−13.0 ± 3.1 (3)

Values are mean ± s.e. mean; figures in parentheses = number of results.

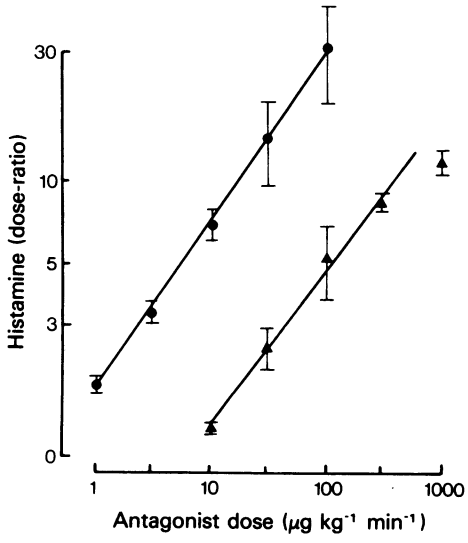

Figure 3 Antagonism of vasodepressor responses to histamine by ranitidine (●) and cimetidine (▲) in the presence of mepyramine. Values are means; vertical lines show s.e. mean.

Therefore ranitidine was 19.2 times more active than cimetidine in these experiments.

Table 3 summarizes the effects of ranitidine alone on depressor dose-response curves to histamine, acetylcholine and (−)-isoprenaline and pressor dose-response curves to phenylephrine. The control and test values used to obtain dose-ratios given in Table 3 were compared using the Mann Whitney U test (2 tailed) and the statistical significance of the effects of ranitidine and the known antagonists were determined. When ranitidine (3 to 300 μg kg^{-1} min^{-1}) was tested in the absence of mepyramine it had no significant effect on the histamine dose-response curve ($P > 0.05$). Furthermore, ranitidine, at doses up to 300 μg kg^{-1} min^{-1} did not significantly affect the vasodepressor response to acetylcholine or (−)-isoprenaline or the vasopressor effect of phenylephrine ($P > 0.05$). However, the dose-response curve to each of these agonists was significantly displaced by an appropriate antagonist i.e. histamine was antagonized by mepyramine ($P < 0.001$), acetylcholine by atropine ($P < 0.05$), (−)-isoprenaline by propranolol ($P < 0.05$) and phenylephrine by phentolamine ($P < 0.05$).

Discussion

The vasodepressor action of histamine has been known for 70 years (Dale & Laidlaw, 1910; 1911) but it was not until the discovery of anti-histamine drugs (H_1-receptor antagonists) that the fall in blood pressure following small doses of histamine could be blocked. However, antagonists of this type could not prevent the fall in blood pressure resulting from the administration of higher doses of histamine. Folkow, Haeger & Kahlson (1948) suggested that one possible explanation was the presence of two types of histamine receptor in the cardiovascular system. Since the discovery of H_2-receptor antagonists it has been established that the postulated second cardiovascular histamine receptor is of the H_2-type (Black *et al.*, 1975; Powell & Brody, 1976). Black *et al.*, (1975) showed that the histamine dose-response curve can be displaced to the right by administration of an H_2-receptor antagonist. We have now compared the actions of ranitidine with those of cimetidine, on both the gastric secretory and vascular responses to histamine.

Ranitidine was a potent inhibitor of histamine-induced gastric acid secretion in the anaesthetized dog whether given as an intravenous bolus or an infusion for 30 min. Ranitidine was qualitatively similar

Table 3 Effects of ranitidine on vasodepressor dose-response curves to histamine, acetylcholine and (−)-isoprenaline and vasopressor dose-response curves to phenylephrine

	Displacement of dose-response curve to right			
	Histamine	*Acetylcholine*	*Isoprenaline*	*Phenylephrine*
Ranitidine 30 μg kg^{-1} min^{-1}	1.17 ± 0.04 (4)	0.97 ± 0.22 (4)	0.83 ± 0.10 (3)	0.94 ± 0.10 (4)
Ranitidine 100 μg kg^{-1} min^{-1}	1.66 ± 0.42 (3)	0.64 ± 0.15 (3)	1.51 ± 0.37 (3)	0.90 ± 0.05 (4)
Ranitidine 300 μg kg^{-1} min^{-1}	2.11 ± 0.31 (3)	0.42 ± 0.10 (3)	2.02 ± 1.10 (3)	0.80 ± 0.06 (4)
Known antagonist	7.71 ± 0.84[a] (15)	6.31 ± 1.73[b] (3)	25.00 ± 5.20[c] (4)	14.40 ± 2.36[d] (4)

Figures in parentheses = number of experiments. Values are mean ± s.e. mean.
[a] Mepyramine 0.7 mg/kg; [b] atropine 10 μg/kg; [c]propranolol 1 mg/kg; [d]phentolamine 1 mg/kg.

to the H_2-receptor antagonist, cimetidine. However, ranitidine is more potent than cimetidine: 9.6 times when administered as an intravenous bolus dose and 4.2 times when administered as an intravenous infusion for 30 min. The difference in relative potency of ranitidine and cimetidine following intravenous infusion or bolus dosing is approximately two fold and might reflect slight differences in the pharmacokinetics of the two drugs. However, since blood levels of the two drugs were not monitored in this study we are unable to substantiate this possibility. Neither ranitidine nor cimetidine have any significant effects on heart rate, blood pressure or respiratory pressure when administered intravenously at doses up to 35 to 40 times the antisecretory ED_{50} values.

Black *et al.* (1975) have shown that mepyramine (0.7 mg/kg) caused a parallel displacement to the right of the histamine dose-response curve with a mean dose ratio of 7.1. This is in agreement with our results which gave a mean dose ratio of 6.95. Black *et al.* (1975) have also shown that increasing the mepyramine dose by ten fold produced no further shift of the histamine dose-response curve. Our studies showed that the H_2-receptor antagonist, ranitidine, alone did not displace the histamine dose-response curve. However, after the maximally effective dose of mepyramine, ranitidine or cimetidine caused further, dose-related parallel displacements of the histamine dose-response curve suggesting competitive antagonism by both H_2-receptor antagonists. In this test ranitidine was 19.2 times more potent than cimetidine.

The lack of effect of ranitidine on vasodepressor dose-response curves to acetylcholine and (−)-isoprenaline and the vasopressor dose-response curves to phenylephrine indicates that ranitidine is a selective antagonist of histamine at cardiovascular H_2-receptors.

In these experiments ranitidine had the same profile of action as the imidazole-based H_2-receptor antagonist, cimetidine. The evidence from this and previous studies is compatible with the hypothesis that the blood pressure response to histamine is mediated through H_1- and H_2-receptors and that there is no need to invoke further receptors such as an H_3-receptor (Chand, Eyre & De Roth, 1979) for this physiological system.

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