administration of dopamine (0.1 mg/kg), secretin (0.2 u/kg), glucagon (0.5 μg/kg) or cholecystokinin (0.15 u/kg) elicited short-lived falls in blood pressure. These depressor responses were similar in magnitude and duration to those of dopamine. Responses to secretin and glucagon were rapidly tachyphylactic, but this effect was reversed following administration of dopamine and could be prevented by alternating doses of dopamine with doses of either hormone. Responses to cholecystokinin did not show tachyphylaxis but did reduce the responses to subsequent doses of dopamine, secretin or glucagon.

Pentagastrin (0.1 μg/kg) evoked short-lived increases in blood pressure. The hypotensive responses to dopamine, secretin, glucagon and cholecystokinin were completely reversed following administration of pentagastrin (0.1 μg/kg) or metoclopramide (5 mg/kg).

These results suggest that secretin and glucagon may have direct or indirect agonist actions at dopamine receptors. Cholecystokinin appeared to behave as a partial agonist, whilst both pentagastrin and metoclopramide acted as dopamine receptor antagonists. The interaction of these hormones with dopamine receptors could be of importance in elucidating some of their effects on vascular haemodynamics or on gastrointestinal motility.

References

DAY, M.D. & BLOWER, P.R. (1975). Cardiovascular dopamine receptor stimulation antagonized by metoclopramide. *J. Pharm. Pharmac.*, **27**, 276–278.

FURUTA, Y., HASHIMOTO, K., IWATSUKI, K. & TAKEUCHI, O. (1973). Effects of enzyme inhibitors of catecholamine metabolism and of haloperidol on the pancreatic secretion induced by L-Dopa and by dopamine in dogs. *Br. J. Pharmac.*, **47**, 77–84.

JACOBY, H.I. & BRODIE, D.A. (1967). Gastrointestinal actions of metoclopramide. *Gastroenterology*, **52**, 676–684.

JAMES, W.B. & HUME, R. (1968). Action of metoclopramide on gastric emptying and small bowel transit time. *Gut*, **9**, 203–205.

The effects of histamine and selective histamine receptor agonists on the isolated working guinea-pig heart preparation

SHEILA B. FLYNN, R.W. GRISTWOOD
D.A.A. OWEN

The Department of Pharmacology, The Research Institute, Smith Kline and French Laboratories Limited, Welwyn Garden City, Hertfordshire

We have recently described an isolated guinea-pig heart preparation capable of sustaining external work (Flynn, Gristwood & Owen, 1977). Using this preparation the effects of histamine and the selective histamine H_1- and H_2-receptor agonists, 2-pyridylethylamine (Durant, Ganellin & Parsons, 1975) and dimaprit (Parsons, Owen, Ganellin & Durant, 1977) respectively, on cardiac function were investigated.

Full dose response curves for each agonist were constructed in separate preparations. Parallel line assays were used to compare the potencies of 2-pyridylethylamine and dimaprit with histamine. The analysis of variance used to estimate potency showed that the dose-response curves to each of the agonists were parallel over the dose-range used.

Control values for each measured parameter after stabilization of the preparations were: external work (E.W.) 0.410 ± 0.017 kg-m min^{-1} g^{-1}, maximum left ventricular pressure (L.V.P. max.) 84.5 ± 1.2 mmHg, contractility as indicated by dL.V.P./dt max. (dp/dt max.) 2239 ± 96 mmHg/s, sinus rate (S.R.) 216.2 ± 4.4 beats/min, aortic flow (A.F.) 360.0 ± 13.8 ml min^{-1} g^{-1}, coronary flow (C.F.) 73.0 ± 4.1 ml min^{-1} g^{-1} and cardiac output (C.O.) 433.1 ± 16.8 ml min^{-1} g^{-1}, ($n = 20$). Where appropriate, measurements are expressed per gram dry weight of heart. These and subsequent figures are means ± s.e. mean.

Histamine increased all measured parameters of cardiac function over the dose-range 10^{-9} to 10^{-6} mol. The maximum absolute increase in each parameter, was calculated from the equation $V = (Vm/1 + K)/A$, where V = response, Vm = maximum response, K = dissociation constant of agonist and A = dose of agonist. The increases were: E.W. 0.353 ± 0.026 kg-m min^{-1} g^{-1}, L.V.P. max. 41.5 ± 2.0 mmHg, dp/dt max. 4132 ± 229 mmHg/s, S.R. 122.9 ± 4.9 beats/min, A.F. 152.7 ± 14.6 ml min^{-1} g^{-1}, C.F. 42.9 ± 4.1 ml min^{-1} g^{-1} and C.O. 188.8 ± 11.9 ml min^{-1} g^{-1}, ($n = 8$).

Dimaprit produced similar changes to histamine in all parameters over the same dose-range. The maximum increase in each parameter was: E.W. 0.422 ± 0.035 kg-m min^{-1} g^{-1}, L.V.P. max. 48.4 ± 6.1 mmHg, dp/dt max. 4398 ± 340 mmHg/s, S.R. 122.8 ± 7.8 beats/min, A.F. 174.5 ± 19.6 ml min^{-1} g^{-1}, C.F. 41.6 ± 1.1 ml min^{-1} g^{-1} and C.O. 211.5 ± 20.1 ml min^{-1} g^{-1}, ($n = 6$).

The potencies, with fiducial limits, of dimaprit relative to histamine (100%) for each parameter, were: E.W. 74.4 (57.2–96.8)%, L.V.P. max. 47.0

(29.3–75.5)%, S.R. 70.9 (50.6–99.4)%, A.F. 64.3 (43.1–95.9)%, dp/dt max. 57.9 (51.3–65.4)%, C.F. 37.2 (22.1–62.4)%, and C.O. 76.9 (51.3–115.3)%.

2-Pyridylethylamine between 10^{-8} and 10^{-6} mol had little effect on sinus rate, increased coronary flow and produced decreases in all other parameters. Doses in excess of 10^{-6} mol and up to 10^{-4} mol elicited increases in all parameters. The maximum increase in each parameter was consistently less than that produced by histamine. For the increases, the potency of 2-pyridylethylamine relative to histamine (100%) on all parameters, was about 0.2%. This could indicate histamine H_2-receptor stimulation, as 2-pyridylethylamine has been shown to have about 0.2% the activity of histamine on a histamine H_2-receptor system (Durant *et al.*, 1975).

The results indicate the importance of histamine H_2-receptors in the mediation of the changes in cardiac function produced by histamine in this preparation. The involvement of histamine H_1-receptors is less clear from this study although the data suggests that they may mediate a selective cardiac depression.

References

DURANT, G.J., GANELLIN, C.R. & PARSONS, M.E. (1975). Chemical differentiation of histamine H_1- and H_2-receptor agonists. *J. Med. Chem.*, **18**, 905–909.

FLYNN, S.B., GRISTWOOD, R.W. & OWEN, D.A.A. (1977). An isolated guinea-pig working heart: preliminary studies with histamine and noradrenaline. *Br. J. Pharmac.*, **59**, 530P.

PARSONS, M.E., OWEN, D.A.A., GANELLIN, C.R. & DURANT, G.J. (1977). Dimaprit—[S-[3-(*N,N*-dimethylamino)propyl]isothiourea]—a highly specific histamine H_2-receptor agonist. Part 1. Pharmacology. *Agents and Actions*, **7**, 31–37.

The effects of four general anaesthetic agents on the regional distribution of cardiac output in the rat

G.J. BELL, C.R. HILEY & M.S. YATES

Department of Pharmacology & Therapeutics, University of Liverpool, P.O. Box 147, Liverpool L69 3BX

The use of radioactive microspheres for the measurement of the distribution of cardiac output (CO) is now an established technique (Rudolph & Heymann, 1967; Mendell & Hollenberg, 1971; McDevitt & Nies, 1976). We have used this technique to compare the cardiovascular effects of four general anaesthetics, sodium pentobarbitone (Sagatal, May & Baker), ethyl carbamate (BDH), alphaxalone/alphadolone acetate (Saffan, Glaxo) and ketamine (Ketalar, Parke-Davis) given intraperitoneally.

Carbonized microspheres (15 μ; 3M Co., St Paul, Minnesota) labelled with ^{85}Sr were injected into the left ventricle of male rats (250–400 g) via a cannula passed down the right carotid artery. Cardiac output and its distribution were determined by the technique of McDevitt & Nies (1976). The results for each anaesthetic are shown in Table 1.

There was no significant difference in the mean cardiac output and arterial blood pressure with the four anaesthetics. Ethyl carbamate produces the most strikingly different distribution of cardiac output when compared to the other three anaesthetics. It produces significant ($P < 0.05$) reductions in flow to the kidneys, spleen, gastro-intestinal tract and in the total hepatosplanchnic flow. Ethyl carbamate also showed a significant increase ($P < 0.05$) in flow to muscle when compared with pentobarbitone and alphaxalone/alphadolone.

Ketamine when compared to the other three anaesthetics produced an increase in flow to the brain. In seven of the animals anaesthetized with ketamine, blood flow to the cerebellum and brain stem, and to each cerebral hemisphere was determined separately. Blood flow to the cerebellum and brain stem was 1.17 ± 0.05 (7), left hemisphere 1.74 ± 0.17 (7) and right hemisphere 1.55 ± 0.13 (7) ml min^{-1} g^{-1}. Thus ligation of the right carotid artery, an integral part of the technique does not significantly reduce flow to the right hemisphere.

Our results indicate that only ethyl carbamate produces a greatly different pattern of distribution of cardiac output compared to the other anaesthetics studied. This may be a consequence of hypersecretion of adrenaline produced by this anaesthetic (Spriggs & Stockham, 1964).

This work was supported by grants from I.C.I. Ltd and Mersey Regional Health Authority. We wish to thank Mr P.J. Roberts for invaluable technical assistance.

References

McDEVITT, D.G. & NIES, A.S. (1976). Simultaneous measurement of cardiac output and its distribution with microspheres in the rat. *Cardiovascular Res.*, **10**, 494–498.

MENDELL, P.L. & HOLLENBERG, N.K. (1971). Cardiac output distribution in the rat: comparison of rubidium and microsphere methods. *Am. J. Physiol.*, **221**, 1617–1620.

RUDOLPH, A. & HEYMANN, M.A. (1967). The circulation of the fetus *in vitro*. *Circulation Res.*, **21**, 163–184.

SPRIGGS, T.L.B. & STOCKHAM, M.A. (1964). Urethane anaesthesia and pituitary-adrenal function in the rat. *J. Pharm. Pharmac.*, **16**, 603–610.