ABILITY OF GLUCAGON TO PRODUCE CARDIAC STIMULATION WITHOUT ARRHYTHMIAS IN HALOTHANE-ANAESTHETIZED ANIMALS

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SUMMARY
The cardiovascular effects of glucagon were determined in cats and dogs anaesthetized with halothane. Glucagon increased heart rate and myocardial contractility but did not produce ventricular arrhythmias. Adrenaline and isoprenaline, which also increased heart rate and myocardial contractility, did produce ventricular arrhythmias. The cardiac stimulant effects of glucagon were not prevented by beta-adrenergic blockade while those of adrenaline and isoprenaline were.

Many of the sympathomimetic agents used during anaesthesia and operation may produce ventricular arrhythmias, particularly when injected during inhalation of halogenated hydrocarbons or cyclopropane (Catenacci et al., 1963; Loehning and Czorny, 1960; Katz and Katz, 1966; Katz and Epstein, 1968). Arrhythmias are more prone to develop when sympathomimetics with a myocardial stimulating action are used. These arrhythmias, which have been attributed to beta-adrenergic stimulation, can be abolished by beta-adrenergic blocking agents. However, beta blockers depress myocardial function and have other undesirable side effects (Katz and Epstein, 1968). An agent which was capable of cardiac stimulation without producing ventricular arrhythmias and which was effective despite beta-adrenergic block would be of clinical value. The present study demonstrates that glucagon is a potent cardiac stimulant, will not produce ventricular arrhythmias in animals anaesthetized with halothane and is also effective in the presence of beta-adrenergic blockade.

METHODS
Fifteen cats weighing 2-4.8 kg were induced either with sodium pentobarbitone (36 mg/kg intraperitoneally) or with 2 per cent halothane in oxygen. Anaesthesia was maintained with 1 per cent halothane in oxygen. All cats inhaled halothane for 30-60 minutes before receiving any drugs. Halothane and oxygen were delivered either from a Kinet-o-meter anaesthesia machine with a Vernitrol vaporizer or else from a Boyle machine with a Fluotec vaporizer.

The trachea, femoral artery and femoral vein were cannulated. All animals were artificially ventilated with a Lee respirator and a Sierra non-breathing valve (No. 28-560) or with a Palmer Ideal Pump. The tidal volume was 12-15 ml/kg and the rate 24-28 b.p.m. which in our laboratory allows arterial pH and Pco\textsc{ii} to be maintained at or near control levels. Spot checks of arterial pH and Pco\textsc{ii} were also made.

Myocardial contractile force was monitored either with a Walton-Brodie strain gauge arch sutured to the right ventricle or by estimation from the pulse pressure. Similar results were obtained with both methods. Femoral arterial pressure was measured with the aid of a Statham pressure transducer. Lead 2 of the electrocardiogram, myocardial contractile force and arterial pressure were recorded on a Grass polygraph, a Devices Recorder or an SE Laboratories ultraviolet recorder.

Nine dogs (greyhound or mongrel) weighing 18-31 kg were also studied. In general the methods...
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were similar to those described above except that anaesthesia was induced with sodium thiopentone 20–30 mg/kg given intravenously and followed by 1 per cent halothane in air. The following drugs were given intravenously: glucagon, isoprenaline, adrenaline and propranolol. Reserpine was given by intraperitoneal injection.

RESULTS

Cat.

In preliminary experiments the dose-response curve of glucagon was determined. A dose of 50 μg/kg was found to produce 80–100 per cent of the maximum effect on heart rate, myocardial contractile force and arterial pressure. This dose was used in subsequent studies. The injection of 50 μg/kg produced a mean increase in heart rate of 27 per cent from a control mean of 167 beats/min. Myocardial contractile force increased 39 per cent. Mean arterial pressure fell 25 per cent from a control mean of 76 mm Hg. Glucagon did not produce ventricular arrhythmias. In order to be sure that arrhythmias were capable of being produced, isoprenaline and/or adrenaline were injected in three cats. Ventricular arrhythmias of 16–20 seconds duration were produced by isoprenaline 2–5 μg/kg or adrenaline 1–2 μg/kg.

The effects of the beta-adrenergic blocker propranolol on the responses to glucagon and isoprenaline were determined in five cats. The intravenous injection of propranolol 0.5 mg/kg did not prevent the increase in heart rate and myocardial contractile force or the fall in blood pressure produced by glucagon 50 μg/kg. The mean increase in heart rate was 24 per cent from a control mean of 143 beats/min; myocardial contractility increased 42 per cent; and mean arterial pressure fell 25 per cent from a control mean of 64 mm Hg. However, propranolol virtually abolished the increase in heart rate and myocardial contractile force and the fall in arterial pressure produced by isoprenaline. In addition, the dose of isoprenaline which, prior to propranolol, produced ventricular arrhythmias no longer did so after injection of propranolol.

In three cats given reserpine 3 mg/kg intraperitoneally 24 hours prior to the study, the intravenous injection of glucagon 50 μg/kg increased heart rate 31 per cent from a control mean of 145 beats/min; increased myocardial contractile force 46 per cent and decreased mean arterial pressure 21 per cent from a control mean of 63 mm Hg. Ventricular arrhythmias were not produced in any of these animals.

Dog.

In preliminary experiments the dose-response curve of glucagon was determined. A dose of 50 μg/kg was found to produce 75–100 per cent of the maximal effect on heart rate, myocardial contractility and arterial pressure. This dose increased heart rate 46 per cent from a control mean of 134 beats/min; increased myocardial contractile force 43 per cent, and decreased mean arterial blood pressure 26 per cent from a control mean of 107 mm Hg. Ventricular arrhythmias were not observed in any of the animals. In order to be sure that ventricular arrhythmias were capable of being produced, adrenaline was injected in three dogs. Ventricular arrhythmias of 15–63 seconds duration were produced by adrenaline 2–4 μg/kg. Pulsus alternans was observed in seven of the nine dogs studied; sometimes occurring prior to the injection of glucagon and sometimes after the injection. In one case pulsus alternans disappeared 1 minute after the injection of glucagon.

Propranolol 0.5 mg/kg did not prevent glucagon from increasing heart rate and myocardial contractility or decreasing arterial pressure in three animals studied. Glucagon produced a mean increase in heart rate of 41 per cent from a control mean of 135 beats/min; myocardial contractility increased 48 per cent, and mean arterial pressure fell 26 per cent from a control mean of 107 mm Hg. Propranolol did block the adrenaline-induced increase in myocardial contractility and heart rate. In addition, propranolol prevented adrenaline from producing ventricular arrhythmias.

DISCUSSION

In 1923 Murlin and associates noted that pancreatic extracts contained a hyperglycaemic factor (HGF) which they named glucagon (Murlin et al., 1923; Kimball and Murlin, 1923–24). Sutherland et al. (1949) purified this hyperglycaemic factor from insulin, obtaining small amounts of a partially purified preparation with significant glucagon activity, but insufficient...
amounts to permit extensive characterization. It remained for Staub, Sinn and Behrens (1953, 1955) to accomplish purification and crystallization of glucagon. These workers were then able to characterize glucagon with respect to its physical and biological properties. Glucagon is a polypeptide hormone (29 amino acid residues; molecular weight 3,485) secreted by the alpha cells of the pancreas. On parenteral injection it increases blood glucose concentration and is therefore used in the treatment of hypoglycaemia, particularly in diabetics in insulin coma.

The cardiovascular effects of glucagon were studied by Farah and Tuttle (1960) who thought that the haemodynamic effects seen with insulin might be due to contamination of the insulin with glucagon. They found that although glucagon had no effect in the intact dog, in the heart-lung preparation it increased heart rate and myocardial contractile force. Although there were a few subsequent reports of the cardiovascular effects of glucagon (Regan et al., 1964; Whitehouse and James, 1966) it is only recently that this agent seems to have become of widespread interest. Lucchesi (1968) and Glick and others (1968) clearly demonstrated that glucagon increased heart rate and myocardial contractility in the intact as well as isolated heart, and that it decreased arterial blood pressure. In these respects it resembles isoprenaline. However, unlike isoprenaline and other catecholamines which produced cardiac arrhythmias when injected during halothane inhalation, we found that glucagon was capable of increasing heart rate and myocardial contractility without producing arrhythmias in animals anaesthetized with halothane.

There has been some controversy over the effects of beta-adrenergic blockers on the increase in heart rate and myocardial contractility produced by glucagon. The glucagon-induced tachycardia has been reported to be blocked by dichloroisoprenaline (Farah and Tuttle, 1960), pronethalol (Whitehouse and James, 1966) and propranolol (Glick et al., 1968). On the other hand, Lucchesi (1968) found that propranolol did not prevent glucagon from increasing heart rate. Concerning myocardial contractility, Farah and Tuttle (1960) and Regan and associates (1964) reported that dichloroisoprenaline blocked the glucagon-induced increase in myocardial contractile force while Lucchesi (1968) and Glick and associates (1968) found that this action of glucagon was not prevented by propranolol. In the present study propranolol did not prevent the increase in heart rate or the increase in myocardial contractility produced by glucagon.

The mechanism of action of glucagon is not clear. It is known that the induced hyperglycaemia is not a factor since prevention of the hyperglycaemia by the injection of insulin does not modify the response to glucagon (Glick et al., 1968). Although glucagon does release catecholamines from the adrenal gland (Scian et al., 1960; Sarcione et al., 1963) this does not appear to be an important factor since we observed, as did others (Farah and Tuttle, 1960; Regan et al., 1964; Lucchesi, 1968; Glick et al., 1968), that the prior administration of reserpine, in doses which deplete the myocardium and adrenals of catecholamines, does not modify the effects of glucagon. The similarity of effects of glucagon and isoprenaline raised the possibility that glucagon might work by stimulation of beta-adrenergic receptors. More specifically it has been suggested (Lucchesi, 1968; Glick et al., 1968) that glucagon may work by stimulating the enzyme adenyl cyclase resulting in an increase in cyclic AMP (adenosine 3', 5'-monophosphate). Both glucagon and catecholamines are known to function in many tissues by stimulating adenyl cyclase and thus increasing cyclic AMP tissue levels (Sutherland, Robison and Butcher, 1968). Recently, it has been reported (Sutherland, Robison and Butcher, 1968) that glucagon increases the level of cyclic AMP in cardiac muscle. However, La Raia, Craig and Reddy (1968) reported in a preliminary communication that glucagon did not increase the level of cyclic AMP in cardiac muscle while isoprenaline did. Furthermore, although the effects of isoprenaline and glucagon are similar, differences were observed in the present study. Unlike isoprenaline, glucagon did not produce arrhythmias nor were its effects blocked by beta-adrenergic blockade. Although the failure of beta-adrenergic blockade to prevent the effects of glucagon might be interpreted as evidence against the action of glucagon being mediated by beta-adrenergic receptors and cyclic AMP, Glick and colleagues (1968) have suggested that the varying results may be accounted for by differences in
receptor responses. At present it is not possible to draw firm conclusions as to the mechanism of action of glucagon on the heart.

The possible clinical value of glucagon, assuming it behaves in man as it does in animals, lies in its ability to stimulate the myocardium without producing arrhythmias. Also of value is the ability of glucagon to stimulate the heart despite beta-adrenergic blockade. This may be of particular importance in view of the increasing use of beta-adrenergic blockers during anaesthesia and the marked cardiovascular depression they produce (Jorfeldt et al., 1967; Katz and Epstein, 1968). In the presence of beta-adrenergic blockade catecholamines have a diminished or absent cardiac activity, but glucagon would still be effective. In addition, glucagon is capable of countering the cardiac depression produced by beta-adrenergic block (Lucchesi, 1968). Another possible advantage of glucagon over catecholamines is that reserpine does not modify the effects of glucagon whereas it produces supersensitivity to catecholamines, resulting in an increased ability to produce cardiac arrhythmias (Fleming, 1962).

Preliminary studies in patients with and without heart disease have demonstrated that glucagon increases cardiac output by 20-30 per cent, and increases heart rate approximately 10 per cent. There was variable change in arterial pressure and a decrease in peripheral resistance (Klein, Morch and Mahon, 1968; Parmley, Glick and Sonnenblick, 1968; Linhart et al., 1968; Parmley, Matloff and Sonnenblick, 1969; Williams et al., 1969). Further studies, in anesthetized patients, seem indicated.

REFERENCES


Few writers seem to have the gift of writing simply, clearly and credibly of the elements of a specialized subject but this facility is certainly given to Drs. Norris and Campbell whose books for nurses, for medical students and residents, have been so deservedly popular of late years. The present volume is the fourth edition of a book first published in 1964. This of itself is adequate testimonial to its established popularity.

The new edition is well up to the standard of its predecessors and the opportunity has been taken to revise the text as a whole and to add a completely new chapter on work in the labour room. This chapter will be of very great value to the nurse who, as part of her general training, has to work in a midwifery unit. It does not, however, contain the information which a pupil midwife will require to satisfy her examiners. But it is fairly clear that it never was the authors' intention to cover the field in this sort of detail. It is for this reason that, for example, only pethidine and morphine are mentioned as opiate analgesics in labour and the actual temperatures at which Entonox separates into its component gases is not accurately defined. Overall, however, the reviewer's reaction to this chapter was to hope that before too long Drs. Norris and Campbell will produce a comparable work for pupil midwives.

A few minor points were noted. The little section on neuroleptanalgesia covered this most difficult subject efficiently and included the necessary warning of the risk of the development of respiratory depression in the postoperative period. The reminder of the need to remove wigs from patients about to have a general anaesthetic—or at least to know that they are there—is timely in view of current trends in fashion. A new risk might also deserve a note, namely the presence of contact lenses, particularly in those admitted after a road traffic accident. It would also appear that Drs. Campbell and Norris's dietitian has been most fortunate in the matter of tube feeds, for she commends one consisting solely of Complan and glucose; it is the reviewer's experience that such a diet sooner or later gives rise to diarrhoea.

It is very heartening to find that though Drs. Campbell and Norris favour the concentration of the intensive therapy of a hospital in a single area, they are fully in line with modern thinking and advise that within this area there should be separate sections for coronary, renal, respiratory and indeed other forms of intensive therapy. Immense harm is being done at present to the concept of intensive therapy by the assumption that all patients who require much nursing care can all be dumped together in a single intensive care unit. Surely by now we ought to have come to realize that the fact that a nurse is competent to manage renal dialysis does not give her any facility in detecting the early signs of malfunction of a ventilator nor yet the ability to distinguish the electrocardiographic changes caused by movement of the patient from those resulting from the onset of ventricular fibrillation.

Over all, this volume fairly lives up to the high standard set by its predecessors and with its numerous illustrations and its comprehensive index it is a model of its kind. We commend it wholeheartedly.

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