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Food Intake of Domestic Fowl Injected With Adrenergic Agonists and Antagonists Into the Hepatic Portal Vein

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HOWES, G. A. AND J. M. FORBES. *Food intake of domestic fowl injected with adrenergic agonists and antagonists into the hepatic portal vein.* PHARMACOL BIOCHEM BEHAV 26(4) 757–764, 1987.—Cockerels of an egg-laying strain were used to study the mode of action of epinephrine on food intake in chickens. Intraperitoneal injection of 2500 μg epinephrine significantly depressed intake from 1–6 hr after injection. This effect was not modified by vagotomy at the level of the proventriculus (equivalent of subdiaphragmatic vagotomy in the mammal). Injection of 25, 50 or 100 μg epinephrine into the hepatic portal vein depressed intake in a dose-related manner. One hundred μg epinephrine had similar effects when injected into the jugular vein as into the portal vein, although the latter injection had longer-lasting effects. As the liver is the major site of inactivation of epinephrine this suggests that it acts mainly at that organ. In order to find which type of receptor is stimulated by epinephrine in its action on feeding an α-adrenergic agonist, phenylephrine, was injected into the portal vein at doses ranging from 63–3000 μg; there was no effect on intake at any dose. A β-adrenergic agonist, salbutamol (500–2000 μg), depressed intake in a dose-related manner following portal vein injection. This effect was not attenuated by vagotomy. Aminophylline, an inhibitor of cAMP breakdown, had no effect on intake when injected into the portal vein (2500–10000 μg) and the depressing effect of 200 μg epinephrine was not modified by simultaneous injection of 10000 μg aminophylline. It is concluded that epinephrine acts on the liver to suppress intake via a vagally-mediated pathway, but that the mechanisms of action are not known.

Chicken Voluntary food intake Epinephrine Vagotomy Salbutamol Aminophylline Phenylephrine

IT has been suggested that there are hepatic receptors for metabolites in mammals and that epinephrine may affect food intake via hepatic metabolism, in particular by effects on glucose metabolism [21]. In humans, food intake activates the sympathetic nervous system [10] and the feeding-induced increase in epinephrine and norepinephrine release into blood might be involved in satiety in the rat [31].

Although the possible role of the liver in the control of food intake has been widely investigated in mammals, there has been much less research with birds. Those studies which have indicated that the avian liver may have a role in intake regulation have mainly looked at the effects of metabolite manipulations [13, 20, 26–28]. There has been very little attention paid to the effects of hormonal manipulations of metabolism on the food intake of birds and it is not known whether any effects are via the liver [13,29]. Adrenaline is released in response to hypoglycaemia [17], and is glycogenolytic in birds [9]. Intraperitoneal injection of 200–1000 μg of epinephrine depressed food intake in chickens, both in free-fed and in 24 hr pre-fasted birds; this was blocked by injection of α- or β-agonists one hour before epinephrine [32].

Epinephrine can bring about its effects by interacting with either α- or β-adrenergic receptors [8]. It was found in mammals that low doses of an α-blocker had no effect on food intake, whereas equal doses of a β-blocker (dichloroisoproterenol) significantly increased the morning intakes for 9–15 days after injection [16]. Administration of catecholamine depletors caused a significant increase in morning intakes for five to eight days after four consecutive injection days. However, if higher doses (1250 μg/kg) were given then a reduced intake was also seen on the injection day. These results suggest a possible physiological action of epinephrine on intake in mammals and that it is probably via β-adrenergic receptors.

The experiments reported here were undertaken to investigate the mechanism of action of epinephrine on the food intake of birds. The first series (Experiments 1 to 4) investigated whether epinephrine is an hepatic satiety factor in birds. These studies involved injections via permanent jugu-

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lar and portal vein catheters in both intact and vagotomised birds, in order to try and determine how specific and localised any effects were. The second series (Experiments 5 to 10) used pharmacological agents to investigate further the mode of action of epinephrine on food intake.

GENERAL METHOD

Male birds of an egg-laying strain were used (404; Mytholmroyd Hatcheries, Hebden Bridge, W. Yorks). Day old chicks were reared in a heated room (33°C reduced to 21°C by week 4) for the first four weeks and were fed on chick starter crumbs (E. B. Bradshaw and Sons Ltd., Bell Mills, Driffield) that contained 180 g protein, 45 g oil, 40 g fibre, 8000 IU vitamin A, 2000 IU vitamin D3 and 10 IU vitamin E/kg. Food intakes were measured to the nearest gramme, spillage being prevented by the use of deep food containers. At four weeks of age the birds were housed separately in metal cages (570 mm high × 510 mm width × 520 mm deep). The room was illuminated for 17 hours each day starting at 0615 hours and environmental temperature was maintained at about 19°C. Water was freely available and birds were fed ad lib (except during surgical procedures) on a commercial feed (Poultry Groaster Pellets; E. B. Bradshaw and Sons Ltd., Bell Mills, Driffield) that contained 145 g protein, 40 g oil, 50 g fibre, 8000 IU vitamin A, 2000 IU vitamin D3 and 10 IU vitamin E/kg.

Surgical Procedures

Hepatic portal vein catheterisation. The technique used was based on modifications [19] made to the general method of Noyan [15]. General anesthesia was induced with equithesin [7] and the feathers plucked off the right flank. The bird was then placed on a board sloped at 30° so that the head was higher than the feet; this was to prevent pulmonary oedema. A veterinary electric blanket was used so as to maintain the body temperature of the bird and room temperature was close to 25°C. An incision was made parallel to the vertebral column and the catheter (500 mm of silicone rubber tubing, 6 mm outside diameter, 3 mm internal diameter; Esco, Broad Street, Teddington, Middlesex; filled with heparinised saline, 100 IU/ml) introduced into the coccygeo-mesenteric vein and advanced to near its convergence with the hepatic portal vein. To accomodate any growth or movement, 150 mm of tubing was left coiled inside the abdominal cavity. The loose end of the catheter was then brought subcutaneously to the back of the head where it was attached to a short length of stainless steel tubing which protruded behind the comb and which was normally occluded with a plastic cap. The abdominal incision was then closed, antibiotic administered and the bird kept in a warm room until it was fully conscious, when it was returned to its cage.

Jugular vein catheterisation. General anesthetic and surgical techniques were similar to those above. Jugular catheters were implanted after portal vein catheters. The incision site (right side lateral mid-neck) was plucked, and the skin cleaned. A 40 mm incision was made parallel with the midline of the neck. The jugular vein was dissected free from any thymus or connective tissue and the silicone rubber tubing was introduced into the vein, advanced to the junction with the vena cava and withdrawn 10 mm. The catheter was again exteriorised at the back of the head and marked to differentiate it from the portal vein catheter.

Abdominal vagotomy. Vagotomy, when performed, was always done after portal vein catheterisation. The bird was layed on its right side and an incision made parallel to the vertebral column just behind the last rib. The vagus nerves were identified as they cross the proventriculus and 10 mm lengths removed to prevent rapid reconnection.

After any surgery, birds were given at least one week for recovery of normal feeding and any surgical procedures were checked at the end of each experiment by dissection. Catheters were flushed daily with 1 ml of heparinised saline (100 IU/ml) and on experimental days 1 ml was also injected into each catheter after every treatment. For all experiments, test solutions were made up fresh each day in sterilised beakers and care was taken not to inject any air bubbles. Injections were made at 1000 hr and treatments were given in a Latin square design unless otherwise stated. Intakes were recorded at frequent intervals for several hours after injection and again 24 hr after injection.

The results were statistically analysed by analysis of variance [14].

EXPERIMENTS AND RESULTS

Experiment 1. The Effect of Intraperitoneal Injections of Epinephrine in Intact and Vagotomised Birds

In birds, the only studies of effects of epinephrine on food intake have used fairly large doses given either intraperitoneally or intramuscularly [13,32]. It was not known whether the epineprhine was acting peripherally or centrally and this experiment was undertaken to see if the anorexia caused by such injections could be attenuated by vagotomy.

Method. Sixteen cockerels aged 17 weeks and weighing 2.3–2.7 kg were used. Half of the birds were vagotomised as described above and the other half were left intact. Each bird received 0 and 2500 μg adrenaline tartrate (Evans Medicals Ltd., Liverpool), referred to henceforth as epineprhine, in 2.5 ml isotonic saline given intraperitoneally on separate occasions in random order with at least 48 hr between.

Results. There was no effect of treatment in the first hour after injection (Fig. 1). Epinephrine significantly reduced food intake in both intact and vagotomised birds from 1 hr to 6 hr. However, a significant difference was seen between vagotomised and intact birds in the 4–5 hour period; after epineprhine treatment vagotomised birds ate significantly more during this hour than similarly treated intact birds. Over 24 hr epinephrine significantly depressed intake of the intact (130.3 vs. 89.3 g) but not of the vagotomised birds (144.3 vs. 116.0 g, s.e.m. 11.4). Birds were observed frequently for several hours after the injection but no signs of malaise were noted in this or any subsequent experiment.

Experiment 2. The Effect of an Intraportal Epinephrine Injection in Intact Birds

This experiment was carried out to see whether an intraportal injection of epinephrine, at doses one tenth to one fourtieth that of the previous experiment, might also reduce intake. This was designed to localise the effect as the liver should inactivate the majority of the lower epinephrine doses and so reduce any general or central nervous system effects [8,30].

Method. Eight cockerels aged 12 weeks and weighing 1.3–1.6 kg were prepared with portal vein catheters as de-

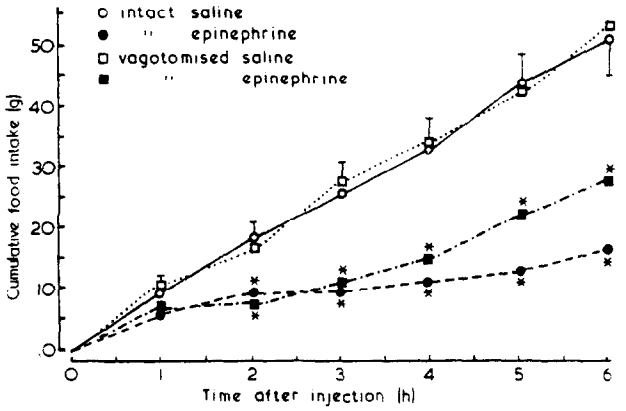

FIG. 1. Mean cumulative food intake (g) of intact and of vagotomised cockerels injected into the hepatic portal vein with isotonic saline with or without 2500 μg epineprhine (Experiment 1). *Difference from control significant at $p<0.05$. Error bar is s.e. of treatment mean calculated from residual mean square of analysis of variance.

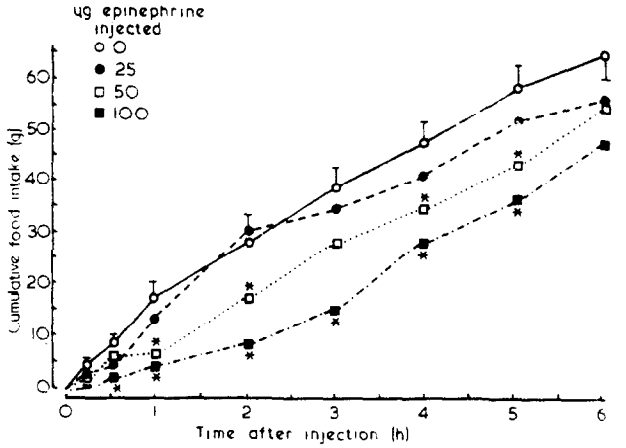

FIG. 2. Mean cumulative food intake (g) after the injection of four levels of epinephrine into the hepatic portal vein (Experiment 2). *Difference from control significant at $p<0.05$. Error bar is s.e. of treatment mean calculated from residual mean square of analysis of variance.

scribed above. On separate occasions the birds received 0, 25, 50 or 100 μg epinephrine in 1 ml of isotonic saline given over 30 sec through the portal vein catheter in an experiment of Latin square design with two replicates. At least 48 hours passed between consecutive treatments in any one bird.

Results. There was a generally dose-related depression in intake with both the 50 and 100 μg epinephrine treatments significantly reducing intake compared with control over the first five hours, but no significant effect was seen after six hours (Fig. 2) or 24 hr (148.3, 140.3, 144.6 and 143.8 g, s.e.m. 10.0, for the increasing doses). The regression equation for intake during the 3 hr after injection (I, g/3 hr±s.d.) against dose (D, μg) is:

$$I = 36.8 - 0.22\ (\pm 0.05)D \qquad (p<0.001)$$

Experiment 3. A Comparison of the Effects of Epinephrine Injected Into the Hepatic Portal Vein or Jugular Vein

The previous experiment showed that epinephrine reduced food intake when injected into the hepatic portal vein but this did not demonstrate the precise site of action. If the effect is not an hepatic one, then it might be expected that a jugular injection of epinephrine would have a larger effect than an intraportal injection, especially if the liver inactivates epinephrine. The site of action of adrenaline was investigated in this experiment by comparing effects of injection into the jugular vein with those of portal vein injection.

Method. Nine birds aged 18 weeks and weighing 2.4–2.8 kg were prepared with hepatic portal vein and jugular vein catheters as described above. Each bird received each of the following three treatments on separate occasions in a Latin square experiment with three replicates: (1) 0.5 ml/kg of isotonic saline injected into both the jugular vein and portal vein; (2) 100 μg epinephrine/kg at a concentration of 200 μg/ml saline injected into the jugular vein and saline injected into the portal vein; (3) The above epinephrine dose injected into the portal vein and saline into the jugular vein.

Results. The effects appeared to be more rapid and transient than in the previous experiments (Fig. 3). At 15 minutes after injection, both jugular and portal vein injection of epinephrine significantly reduced intake. By 60–90 min the effect of jugular injection of epinephrine was no longer significant whereas portal vein injection was still exerting a significant effect.

Experiment 4. The Effect of Epinephrine Injected Into the Hepatic Portal Vein of Vagotomised Birds

Although the results of Experiment 1 showed no great attenuating effect of abdominal vagotomy on the intake inhibition caused by an intraperitoneal injection of a large dose of epinephrine, experiments in mammals [34,35] showed that the effects of lower doses of epinephrine could be attenuated by subdiaphragmatic vagotomy. This experiment was performed to see whether vagotomy at the level of the proventriculus in birds (equivalent to subdiaphragmatic vagotomy in mammals) would block the effects of intraportal injections of lower doses of epinephrine, as used in Experiment 2.

Method. Six cockerels aged 13 weeks and weighing 1.5–1.9 kg were prepared with portal vein catheters and vagotomised as described above. The treatments, imposed in an experiment of Latin square design with two blocks, were given twice to each bird; after the first run one catheter became blocked so this bird could not be used again. The doses of epinephrine were 0, 25, 50 and 100 μg.

Results. None of the treatments caused a significant reduction in food intake (Fig. 4).

Experiment 5. The Effect of Phenylephrine Injection Into the Hepatic Portal Vein of Intact Birds

In order to see whether any effects of epinephrine are via α-adrenergic receptors this experiment examined the effects of phenylephrine which acts on both α-1 and α-2-adrenergic receptors [8].

Method. Five cockerels aged 16 weeks and weighing 2.3–2.6 kg were prepared with hepatic portal vein catheters

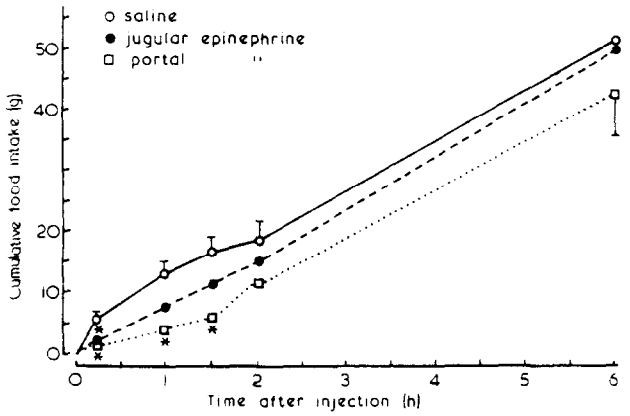

FIG. 3. A comparison of mean cumulative food intakes (g) after injection of 100 μg/kg epinephrine into either the jugular or portal vein, with those after injection of an equal volume of saline to both sites (Experiment 3). *Difference from control significant at $p<0.05$. Error bar is s.e. of treatment mean calculated from residual mean square of analysis of variance.

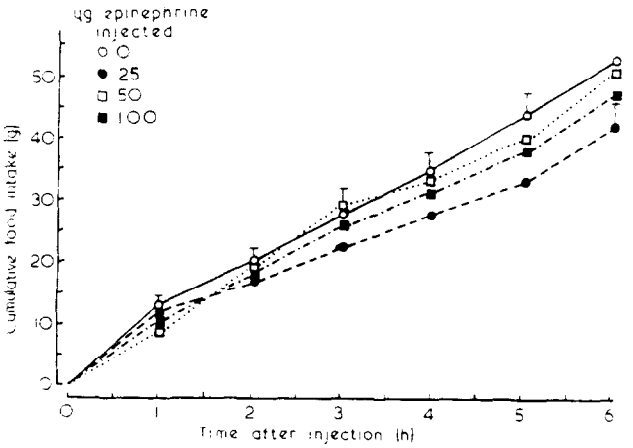

FIG. 4. Mean cumulative food intake (g) after the injection of four levels of epinephrine into the hepatic portal vein of vagotomised cockerels (Experiment 4). Error bar is s.e. of treatment mean calculated from residual mean square of analysis of variance.

TABLE 1

MEAN CUMULATIVE FOOD INTAKE (g) AFTER INJECTION OF FOUR LEVELS OF PHENYLEPHRINE INTO THE HEPATIC PORTAL VEIN (EXPERIMENT 5)

Time From Injection	Amount of Phenylephrine Injected (μg/bird) 0	62.5	125	250	s.e.m.
1 hr	11.3	12.6	14.4	12.5	±1.42
2 hr	21.8	20.8	23.6	24.2	±1.98
3 hr	29.8	29.1	36.9	32.8	±2.38
4 hr	36.7	37.0	45.3	41.5	±2.37
5 hr	46.5	42.8	53.6	48.5	±2.75
6 hr	54.2	51.6	62.2	58.4	±2.87
24 hr	167.5	164.4	174.7	165.0	±4.92

None of the results are significantly different from control.

TABLE 2

MEAN CUMULATIVE FOOD INTAKE (g) AFTER INJECTION OF FOUR LEVELS OF PHENYLEPHRINE INTO THE HEPATIC PORTAL VEIN (EXPERIMENT 6)

Time From Injection	Amount of Phenylephrine Injected (μg/bird) 0	750	1500	3000	s.e.m.
1 hr	9.7	8.2	5.8	5.9	±2.07
2 hr	20.1	17.4	14.1	15.3	±3.00
3 hr	27.6	24.4	26.1	22.8	±3.37
4 hr	33.3	32.9	32.2	31.7	±3.75
5 hr	40.0	44.2	42.2	40.6	±3.88
6 hr	51.9	56.3	49.2	51.1	±4.14
24 hr	142.1	157.0	157.7	163.1	±6.84

Within each time period none of the results are significantly different.

as described above. The birds were given 0, 63, 125 and 250 μg phenylephrine in 1 ml of isotonic saline. These doses were chosen in relation to the doses used intravenously for the treatment of hypotension in humans, where an injection of 800 μg is given, but as the site of injection is more specific here it was decided to use less [8]. The experiment was repeated on the same birds so that the data presented are the mean of ten intakes.

Results. None of the treatments had any significant effect on food intake at any time (Table 1).

Experiment 6. The Effect of Higher Dose Phenylephrine Injection Into the Hepatic Portal Vein of Intact Birds

Method. Five cockerels aged 19 weeks and weighing 2.8–3.1 kg were prepared with portal vein catheters as described above. The experiment was repeated on the same birds, but one of the birds developed a blocked catheter after the first run through so that mean intakes are those of nine values. The injections were of 0, 750, 1500 and 3000 μg phenylephrine in 1 ml isotonic saline.

Results. Again, no dose of the drug had any significant effect on food intake at any time, when compared with the control injection (Table 2).

Experiment 7. The Effect of Salbutamol Injection Into the Hepatic Portal Vein of Intact Birds

As the doses of phenylephrine used in Experiment 6 had no significant effect on food intake, it was decided to see whether the injection of a β-2-adrenergic agonist affected

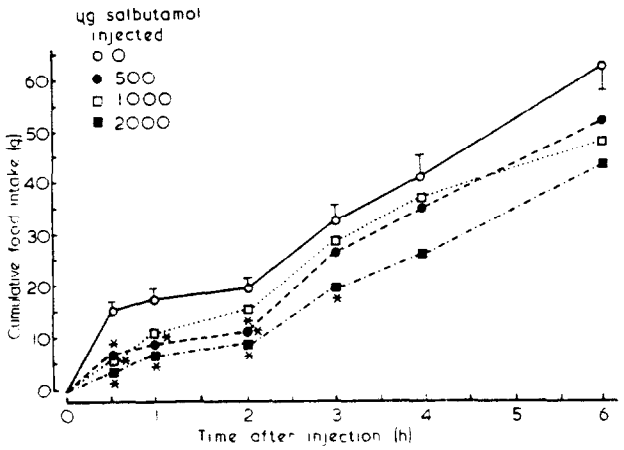

FIG. 5. Mean cumulative food intake (g) after the injection of four levels of salbutamol into the hepatic portal vein of intact birds (Experiment 7). *Difference from control significant at $p<0.05$. Error bar is s.e. of treatment mean calculated from residual mean square of analysis of variance.

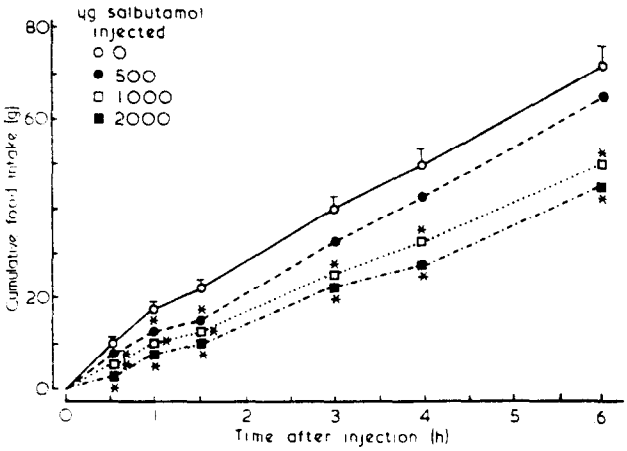

FIG. 6. Mean cumulative food intake (g) after the injection of four levels of salbutamol into the hepatic portal vein of vagotomised birds (Experiment 8). *Differences from control significant at $p<0.05$. Error bar is s.e. of treatment mean calculated from residual mean square of analysis of variance.

food intake. Salbutamol was chosen as it is a fairly specific β-2-agonist and does not have a large β-1 effect on the heart [8].

Method. Five cockerels aged 18 weeks and weighing 2.3–2.7 kg were prepared with hepatic portal vein catheters as before. The experiment was repeated on the same birds so that mean intakes are the mean of ten intakes. The birds received 0, 500, 1000 and 2000 μg of salbutamol (provided by Glaxo Laboratories Ltd., Greenford Road, Greenford, Middlesex) in 1.5 ml of isotonic saline on separate occasions. These doses were chosen in relation to the doses of phenylephrine used in Experiment 6 and also to the doses used in asthma treatment for humans [8].

Results. Salbutamol significantly reduced food intake at the 2000 μg dose and there was a trend for the intermediate doses to depress intake also. The significant effect lasted for three hours (Fig. 5). The regression equation for the relationship between intake (I, g/3 hr) and dose (D, μg±s.d.) was:

$$I = 31.2 - 0.0056\ (+0.0020)D \qquad (p<0.05)$$

Twenty-four hr intakes tended to fall with increasing doses of salbutamol (140.7, 131.6, 128.5, 126.1, s.e.m. 3.2) but this was not significant.

Experiment 8. The Effect of Salbutamol Injection Into the Hepatic Portal Vein of Vagotomised Birds

Experiment 7 showed that salbutamol can reduce food intake, but did not indicate the site of action. Salbutamol also reduces food intake in mammals and it seems to bring about its effects primarily by central actions [3]; 2000–2500 μg/kg of salbutamol injected intraperitoneally into rats reduced intake and injection of very low levels of a beta blocker intracerebroventricularly (100 μg dl-propranolol) prevented this effect, indicating a mainly central action [4]. It was hoped that low enough levels (up to 10 times less) had been injected in Experiment 7 to a localised site to prevent central actions. This experiment was undertaken to see whether abdominal vagotomy attenuated the effects of salbutamol seen in Experiment 7, which would suggest a visceral, possibly hepatic, action.

Method. Six birds aged sixteen weeks and weighing 2.1–2.5 kg were prepared with hepatic portal vein catheters and vagotomised as described above. The experiment was repeated on the same birds but one of the birds developed a blocked catheter after the first run; mean intakes are, therefore, the means of 11 values. The experimental design, except for vagotomy, was identical to Experiment 7.

Results. Vagotomy did not attenuate the effects of salbutamol on food intake (Fig. 6). Cumulative intakes were significantly reduced from 30 minutes onwards for the first six hours, but 24 hour intakes were not significantly affected by treatment (179.1, 184.9, 175.0 and 163.9, s.e.m. 8.6, for the doses in increasing order). The effects were greater and more prolonged than in the intact birds in Experiment 7.

Experiment 9. The Effects of Aminophylline Injection Into the Hepatic Portal Vein of Intact Birds

Theophylline is a competitive inhibitor of certain forms of cyclic nucleotide phosphodiesterase, the enzymes that catalyse the conversion of cAMP to 5'-AMP. Thus, if epinephrine acts by a cAMP-dependent system then theophylline would be expected to potentiate its effects [8]. The next two experiments were undertaken to investigate whether action of epinephrine is by a cAMP-dependent mechanism. Aminophylline was used as it is a more soluble form of theophylline; it is a combination of theophylline with the therapeutically inert ethylene diamine. This experiment was designed to be a pilot experiment for Experiment 10, so as to find a dose of aminophylline that might potentiate the effects of epinephrine but not cause any large effects on its own.

Method. Six birds aged 12 weeks and weighing 1.4–1.8 kg were prepared with hepatic portal vein catheters as described above. The following treatments were given on separate occasions with at least 48 hr between each: 0, 2500, 5000 and 10000 μg aminophylline (Antigen Ltd., Roscrea, Ireland) in 1.5 ml of saline. These doses were chosen from the dosage

TABLE 3

MEAN CUMULATIVE FOOD INTAKE (g) AFTER INJECTION OF FOUR LEVELS OF AMINOPHYLLINE INTO THE HEPATIC PORTAL VEIN OF INTACT BIRDS (EXPERIMENT 9)

Time From Injection	Amount of Aminophylline Injected (μg/bird) 0	2500	5000	10000	s.e.m.
30 min	14.2	11.3	16.0	11.0	±3.31
60 min	18.8	14.5	21.5	17.2	±4.41
90 min	22.5	19.3	30.3	24.0	±4.32
2 hr	27.2	23.5	33.2	27.5	±4.72
4 hr	39.0	39.8	49.2	49.0	±6.03
6 hr	62.7	58.2	68.2	66.2	±6.15
24 hr	160.3	165.3	177.3	170.7	±11.30

Within each time period none of the results are significantly different.

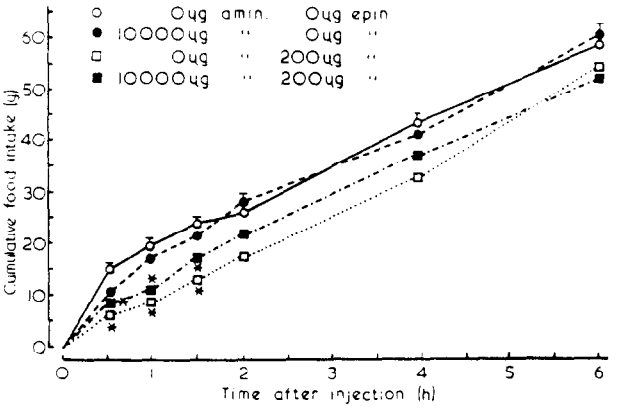

FIG. 7. Mean cumulative food intake (g) of intact birds after injection into the hepatic portal vein of either 0 or 10000 μg aminophylline at the same time as either 0 or 200 μg epinephrine (Experiment 10). *Difference from control significant at $p<0.05$. Error bar is s.e. of treatment mean calculated from residual mean square of analysis of variance.

of theophylline used for intravenous treatment of asthmatic patients, where about 5000 μg/kg is given [8]. As the route of administration was intraportal, it was believed this would lead to fairly high hepatic levels.

Results. At no time did any of the treatments have a significant effect on food intake when compared with control (Table 3).

Experiment 10. Intraportal Injection of Epinephrine and Aminophylline

This experiment was designed to see whether aminophylline would potentiate the effects of epinephrine on food intake, thus indicating a cAMP-dependent action for epinephrine.

Method. Seven birds aged 13 weeks and weighing 1.5–2.0 kg were prepared with hepatic portal vein catheters as described above. The experiment was repeated on the same birds so that the mean intakes are those for 14 values. The birds were given the following treatments on separate occasions: (1) 1.5 ml isotonic saline; (2) 10000 μg aminophylline/bird in 1.5 ml of saline; (3) 200 μg epinephrine/bird in 1.5 ml of saline; (4) 10000 μg aminophylline and 200 μg epinephrine/bird in 1.5 ml of saline.

Results. The data show that both epinephrine and a combined epinephrine and aminophylline injection significantly reduced intake over the first 90 minutes after injection (Fig. 7). At no time did the combined epinephrine and aminophylline treatment significantly reduce intake more than just the epinephrine treatment. In fact, there is not even a trend of any potentiation and at 90 minutes only the epinephrine treatment still caused a significant reduction in food intake.

GENERAL DISCUSSION

Experiment 1 showed that the intraperitoneal injection of 2500 μg of epinephrine reduced food intake in ad lib fed birds; this agrees with previous similar work [13,32]. Large doses of epinephrine make rats sick [5] and although no evidence of malaise was noted in any of the experiments reported here, nor in that of Sykes [32], it is possible that non-specific, extra-hepatic effects of epinephrine were affecting food intake. It has recently been shown that glucose infused into the hepatic portal vein of rats at physiological rates depresses intake but that preference for food of the flavor available during the infusion was subsequently increased, showing that this manipulation of liver glucose availability did not condition an aversion to food [33]. If epinephrine is exerting its action on feeding in the chicken through glucose metabolism then this evidence from the rat might suggest that it is not via an aversive effect.

Site of Action

When lower doses of epinephrine (25–100 μg/kg) were injected into the portal vein there was a dose-related depression of food intake with complete recovery within five hours (Experiment 2). This is in contrast to Experiment 1 where significant effects persisted for 24 hours in the intact birds. These results do not indicate where epinephrine is acting, but the liver would be a good candidate as the injection is fairly specific and much of the epinephrine is likely to be inactivated there.

Portal vein injection of 100 μg/kg of epinephrine had only a slightly greater effect than the same amount given into the jugular vein (Experiment 3). This might at first sight suggest that the effect is not specifically on the liver. However, the fact that the liver is likely to inactivate much of an epinephrine dose [8,30] indicates that the liver is probably an important site of action for the reduction in intake seen at these lower dose levels. We speculate that if the major site of action of epinephrine were not in the liver then a jugular injection would have a very much greater effect than one into the hepatic portal vein.

Vagal Involvement

Vagotomy did not prevent the effect of a large intraperitoneal dose of epinephrine (Experiment 1) although intake tended to recover more quickly, suggesting that a small part of the effect of epinephrine administered in this way on intake is mediated by the vagus nerves. The effects of intraportal epinephrine injection were largely attenuated by

abdominal vagotomy. During the first two hours after injection vagotomised birds (Experiment 4) ate approximately double the amounts eaten by intact birds after the injection of 100 μg/kg (Experiment 2), even though control intakes were slightly lower.

Although the birds in Experiment 4 (vagotomised) were heavier than those in Experiment 2 (intact) and the same doses of epinephrine per bird were given, there was a sufficiently wide range of doses to ensure that the lower dose per unit of body weight was not the reason for the relative lack of effect after vagotomy. It is clear that vagotomy has blocked the effect of epinephrine injected into the portal vein on food intake. The effects of a glucose and lysine infusion into the portal vein of chickens are blocked by vagotomy [20] which, together with the results of the experiments reported here, suggest that the epinephrine response is via receptors in the liver and that the effect is at least partly mediated by vagal afferents. However, some recent work with rats involving selective denervation of the liver has shown no attenuation of the depressing effects of 12.5–100 μg/kg [11] or 30 μg/kg [2] epinephrine on intake.

Vagotomy alters the meal pattern of chickens [20,24] without affecting total daily intake. It appears that the vagotomised birds in Experiment 4 ate less in the middle of the day than the intact birds in Experiment 2 which accounts for the differences in control intakes between intact and vagotomised birds.

Vagotomy did not attenuate the effects of salbutamol (Experiment 8). This indicates that the effect is either central, or that a peripheral effect is not mediated by the vagus to any great extent.

Possible Mode of Action

If epinephrine has an hepatic action then it would appear to be via α- or β-2 receptors [8]. The effect of an intraperitoneal injection of 200–1000 μg of epineprhine per bird is to cause anorexia for several hours and this is prevented by prior treatment with either α- or β-adrenergic receptor blocking agents [32]. The intraportal injection of the α-adrenergic agonist phenylephrine (500–2000 μg/kg) was found to cause no significant reduction in food intake (Experiments 5 and 6). On the contrary, the intraportal injection of the β-agonist salbutamol (500–2000 μg/kg) did cause a significant, dose-related reduction in food intake (Experiment 7). This suggests that the effect of epinephrine is mostly via β-2 receptor interactions, agreeing with the results for mammals, where the hepatic effect of epinephrine is thought to be predominantly via the β-receptors [16]. Salbutamol can affect feeding via a central action, as it can cross the blood-brain barrier more easily than epinephrine and it is likely that the levels used in this experiment were large enough to cause central effects [4]; also salbutamol is broken down more slowly than epinephrine by the liver so that its concentration in the general circulation will remain higher. Such a central action would override any vagally-mediated peripheral action and not be blocked by vagotomy. It would be interesting to see whether prior treatment with an α- or β-antagonist might prevent the effects of an intraportal epinephrine action; this might indicate the hepatic receptor type more specifically than the experiments undertaken here.

Epinephrine is rapidly broken down by the liver and it is surprising that the effects of a single injection lasted for several hours. Possibly the action is after uptake and activation of a second messenger [6], which in the case of the chicken might be cyclic AMP (cAMP) [1]. Experiment 9 demonstrated that the phosphodiesterase inhibitor aminophylline (which inhibits the breakdown of cAMP) does not affect food intake when injected intraportally at 2500–10000 μg. This highest dose did not potentiate the effects of an intraportal injection of 200 μg of epinephrine (Experiment 10). These observations thus give no support to the idea that epinephrine acts via a cAMP-dependent system to affect food intake. Adrenaline has been suggested to have many possible mechanisms of action in mammals [18]. However, a cAMP-dependent mechanism is likely in the avian liver [1] and further work will be necessary to elucidate the mode of action.

A Physiological Role for Epinephrine?

The levels of epinephrine used here were close to those used in mammalian studies [35]. Whether such levels of epinephrine are physiological is doubtful, although if hepatic chromaffin cells do exist in birds, as in mammals, then perhaps quite high local levels of epinephrine could be expected in the hepatic microcirculation [12]. If epinephrine has a physiological role in the control of intake via the liver then presumably there is a reflex secretion of high levels of epinephrine into the hepatic microcirculation as a response to signals originating from various parts of the alimentary tract. Such a mechanism has been suggested in mammals [12, 22, 25] and might well exist in birds.

In deciding whether hepatic epinephrine is likely to be important in the control of intake in normal birds we need to remember that in the ad lib state birds will generally eat briefer but more frequent meals than mammals with a similar diet [23]. Between meals it is unlikely that there would be large changes in circulating metabolites so that physical distension and rate of passage of the food would have an important part to play. Large hepatic changes would not be expected between such frequent meals and this might argue against an hepatic role in intake control in these circumstances. Similarly, hormonal changes during or between frequent meals might not be sufficiently clear-cut or large enough to control feeding. It has been found, however, that small meals taken by rats after a short (1.5 hr) fast cause significant releases of epinephrine and norepinephrine, as well as of insulin and free fatty acids [31] which might have effects on the liver similar to those caused by adrenergic agonists in the work reported here.

In conclusion, epinephrine appears to have an hepatic action on food intake in chickens but the mechanisms have not been clearly elucidated and the significance of such an action in the control of normal feeding is unclear.

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