Br. J. Pharmac. Chemother. (1967), **31**, 290–312.

EFFECT OF SYMPATHOMIMETIC AND ALLIED AMINES ON TEMPERATURE AND OXYGEN CONSUMPTION IN CHICKENS

BY

D. J. ALLEN AND E. MARLEY

From the Institute of Psychiatry, Maudsley Hospital, Denmark Hill, London

(*Received June* 12, 1967)

The sympathomimetic and allied amines can be divided into two main groups according to their chemical structure and to their effects in young chickens (Key & Marley, 1962; Dewhurst & Marley, 1965a, b). These groups are similar to those into which the amines are divided for their effects on smooth muscle (Fleckenstein & Burn, 1953; Burn & Rand, 1958; Maxwell, Povalski & Plummer, 1959; Vane, 1960; Marley, 1962; Trendelenburg, 1963) and this division clearly implies a fundamental difference in mode of action. In young chickens, catecholamines evoked sleep, whereas amphetamine-like amines and some tryptamines had the opposite effect and produced arousal (Key & Marley, 1962; Dewhurst & Marley, 1965a, b). The present experiments were made to determine the effects of these amines on temperature and oxygen consumption.

Our results, a brief account of which was given to the Physiological Society (Allen & Marley, 1966), agree with those of Feldberg & Myers (1963, 1964a, 1965) who found that adrenaline and noradrenaline injected intraventricularly in cats lowered body temperature, whereas 5-hydroxytryptamine raised it.

METHODS

Animals

Rhode Island Red pullets, 1–23 days old and weighing 30 to 150 g, and adult fowls of 1 to 2 kg were used, all from the same hatchery. For the first week after hatching they were kept in a cage thermostatically maintained at 33 to 34° C and for the subsequent 2 weeks at 29 to 31° C. Adult fowls were kept at room temperature.

Anaesthesia

For implanting canulae, electrodes and thermistors, chickens were anaesthetized with halothane (Fluothane, ICI) in oxygen 1.5% v/v., delivered from a Goldman vaporizer as described by Marley & Payne (1964).

Operative procedures

A midline scalp incision and a lateral incision in the neck were made. A polyethylene catheter, 120 cm in length filled with heparin-saline and having an internal volume of less than 0.15 ml., was tied into a jugular vein. In a few chickens the catheter was implanted under the skin with its tip overlying the lumbar vertebrae, or was passed through an incision in the lateral abdominal muscles so that its tip lay within the abdominal cavity. The rest of the tubing was brought under the skin to emerge at the rear of the scalp incision and was fixed to the cranium with Simplex

autopolymerizing acrylic resin (Dental Fillings Ltd.). An adapter was tied into the end of the tubing so that injections could be given into it. Thermistors were implanted, one in the posterior mediastinum (core temperature) and one under the dorsal skin between the scapulae (surface temperature). The thermistors were connected by 120 cm lengths of enamelled copper or copper-nickel wire (S.W.G. 34) to an external thermistor thermometer (Grant Instruments Ltd.), the thermistor leads being brought under the skin to emerge at the scalp where they were fixed to the skull with resin. The thermistor leads and cannula tubing were twisted into a strand long enough for the animal to move freely. The resistance of the thermistors was sufficiently large (3 kΩ) to make their responsiveness independent of the resistance of the leads. In some chickens, cortical and electromyographic recording electrodes were also implanted (Key & Marley, 1962). Operative procedures were complete within 60 min.

Post-operative care

The chickens were conscious within 10 min of stopping the anaesthetic and were kept in a draught-free ventilated recovery box for at least 24 hr before tests were made. Food and water were available. Temperature is influenced by the calorific value of foods (Robinson & Lee, 1947) and all chickens received the same diet of Baby Chick Crumbs, V.A. (Pauls Foods). The temperature of the thermostatically controlled cage (29–31° C) and recovery box (29–31° C) was similar to that of the metabolism chamber (31° C unless otherwise stated in the text) in which most experiments were made.

Testing arrangements

Chickens were studied in a modified Richards & Collison (1928) metabolism chamber. The Perspex chamber was saturated within by water, submerged in a water bath and allowed to reach thermal equilibrium for a minimum of 2 hr before starting the experiment. The thermoneutral range in young featherless chickens appears to be within environmental temperatures of 31°–34° C (Sturkie, 1954a). Bath temperature was maintained with an accuracy of ±0.01° C. The temperature of the metabolism chamber was compared with that of the bath in a number of experiments at 16°, 25°, 28°, 31° and 34° C and they corresponded.

When the chamber had reached thermal equilibrium it was partly lifted from the bath and supported on a bracket. The lid of the chamber was removed and the chicken taken from the recovery box and placed in the chamber. A small slit was made in a rubber teat and the electrodes and cannula brought through the slit; the teat was then fitted over a hole in the lid and the leads and cannula fixed to the teat with celloidin to form an airtight seal. The procedure took about 5 min. The chamber was re-submerged in the bath and left at least 30 min to re-establish thermal equilibrium. The chamber (volume 2460 ml.) was next sealed from the atmosphere and 100 ml. air withdrawn and replaced by oxygen through an oil valve.

As the oxygen in the metabolism chamber was used by the chicken it was replaced by oxygen entering the chamber *via* an oil valve as a series of bubbles of about 1 ml. volume. The changes in pressure in the chamber due to oxygen consumption were recorded by a micromanometer (Devices Sales Ltd.). Each bubble of oxygen entering the chamber was registered as a sharp upstroke on the trace. This method of registration was considerably more sensitive than with a tambour, used in a few experiments. Oxygen consumption was calculated by counting the number of bubbles entering the chamber during successive 10 min periods. Experiments using the chamber were made at 100% humidity, but absolute values for oxygen consumption are expressed as ml. O_2/kg/min (at 760 mm Hg; O° C, and dry). Carbon dioxide formed was drawn into a chamber containing soda lime (Carbosorb B.D.H.), by a fan (1400 rev/min) which penetrated the roof of the chamber through an air- and water-tight shaft with mercury and oil seal.

The temperature of the chicken was recorded at 5 min intervals; it was usually stable within 60 min. No injections were made until the chicken's temperature had been steady for 30 min. Saline, 0.3 ml., at the same temperature as that of the chicken was then slowly injected through the implanted cannula. This sometimes led to a fall in temperature of up to 0.5° C lasting 5 to 10 min. Within the next 30 to 60 min the drug was injected in a volume which together with the wash-in saline amounted to 0.3 ml., and was at the same temperature as that of the chicken. If the chicken's temperature did not stabilize or if the fall of temperature with the saline exceeded 0.5° C then the

experiment was discontinued. By making injections *via* the implanted cannula, the effects of drugs were studied without handling the chickens or disturbing the equilibrium conditions in the metabolism chamber.

Additional experiments were made with chickens at substantially lower environmental temperatures. In one set of experiments the low temperature was maintained throughout the day. In another set of experiments recordings were first made for 120 min with the chicken in the chamber maintained at 31° C. The chamber was then opened to the atmosphere and transferred, with the chicken inside, to a second water bath at 15° or 16° C. After 50 or 60 min the chamber was again sealed from the atmosphere and 100 ml. air withdrawn and replaced by oxygen. Temperature and oxygen consumption were then recorded for 120 min, after which the chamber and its contained chicken were returned to the water bath at 31° C to allow recovery.

Since older fowls were too large to be placed in the oxygen consumption chamber they were studied at room temperature. A few selected younger chickens were also studied at room temperature and body temperature measured by a mercury thermometer inserted 2.5 cm into the rectum from the cloacal orifice.

Chamber air composition

The pO_2 and pCo_2 content of the chamber was analysed in six experiments. In two, the chickens were not given drugs and air samples (about 10 ml.) were taken 1, 2 and 4 hr after sealing the chamber. In the remainder, the chickens were given dexamphetamine (2 μ-mole/kg) and air was withdrawn immediately before and after the injection and 5 hr later. Oxygen was measured with the Beckman Oxygen Analyser and with the Haldane Gas Analysis apparatus; carbon dioxide was determined with the Haldane apparatus. The pO_2 and pCo_2 concentrations of all samples were close to atmospheric with extremes of 140 to 180 mm Hg for oxygen and 0.6 to 0.9 mm Hg for carbon dioxide.

Drugs

These (with molecular weights of salts in parentheses) were the hydrochlorides of (−)-α-methyl noradrenaline [(−)-2-amine-1-(3,4-dihydroxyphenyl) propan-1-ol; (−)-Cobefrine] (220); (±)-α-methyl noradrenaline; (−)-α-methyl adrenaline (234); cocaine (340); (+)- and (±)-α-methyltryptamine (210); phenoxybenzamine (340); phenethylamine (157); 1,2,3,4-tetrahydronaphthylamine (181); tryptamine (196); the sulphates of dexamphetamine (385) and of (±)-tuaminoheptane (328); and the bitartrates of (−)-adrenaline (333) and of (−)-noradrenaline (319). Also used were methysergide (470), mebanazine oxalate-(±)-α-methyl benzyl hydrazine (220); and pentobarbitone sodium. The doses are given in μ-mole/kg, except for pentobarbitone sodium. All injections were intravenous unless otherwise stated.

RESULTS

Oxygen consumption and temperature

Recordings were made of oxygen consumption in chickens aged from 2 to 16 days kept at environmental temperatures of 22°, 25°, 28°, 31° and 34° C. The range of age was that over which the effects of the amines was mostly to be studied. None of these chickens had implanted cannulae or electrodes. The results shown in Fig. 1A are for the mean oxygen consumption (ml./kg/min) measured over 6½ hr (10.30 a.m. to 5 p.m.) each point representing the results from 4 chickens. Oxygen consumption was variable over the first 5 days, but thereafter it gradually declined with increase in age (Fig. 1). After the fifth day lower environmental temperatures led to a higher oxygen consumption. The oxygen consumption after the fifth day for chickens at environmental temperatures of 31° and 22° C differed significantly ($P<0.001$) from each other, showing that 22° C lay outside the thermoneutral range.

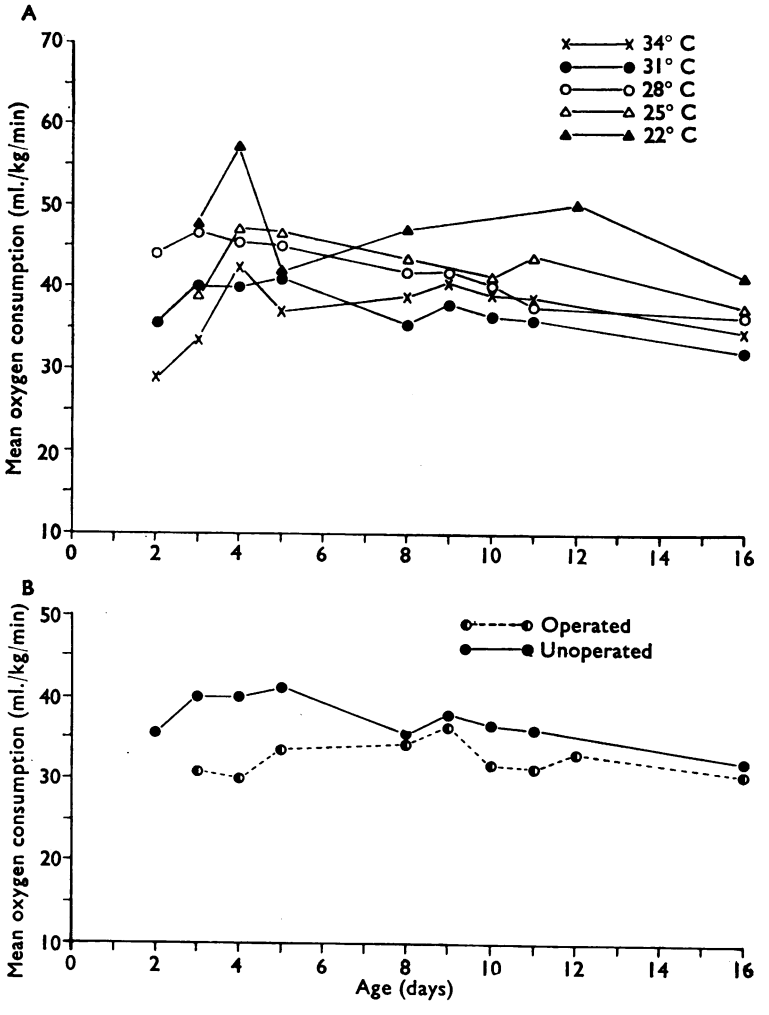

Fig. 1. Graphs of mean oxygen consumption in A for unoperated chickens aged 2 to 16 days and maintained in an oxygen consumption chamber at 22°, 25°, 28°, 31° or 34° C, and in B for unoperated and operated chickens over the same age range but maintained at 31° C. In A and B each point is the mean oxygen consumption in ml./kg/min measured over $6\frac{1}{2}$ hr for 4 chickens. Standard errors not shown, but ranged from 0.10–0.78.

Oxygen consumption in operated chickens

Since experiments were to be made in chickens with implanted thermistors and cannulae (operated chickens), oxygen consumption was next measured over the same period of time in operated chickens kept at 31° C (Fig. 1B). A similar decline in oxygen consumption was observed. The mean oxygen consumptions for operated birds were generally lower than those for the unoperated and the mean values differed significantly except for the results on the eighth, ninth and sixteenth days.

Temperature in operated chickens

Chickens, like mammals, exhibit diurnal variation in body temperature. To find the extent of this during the experimental period, temperature was recorded over the $6\frac{1}{2}$ hr in 6 chickens of various ages maintained at 31° C; temperature varied mostly in the first 90 min of recording but thereafter the variations usually did not exceed 0.5° C. Temperature over this period was therefore sufficiently constant to be used as a baseline from which to measure induced changes in temperature.

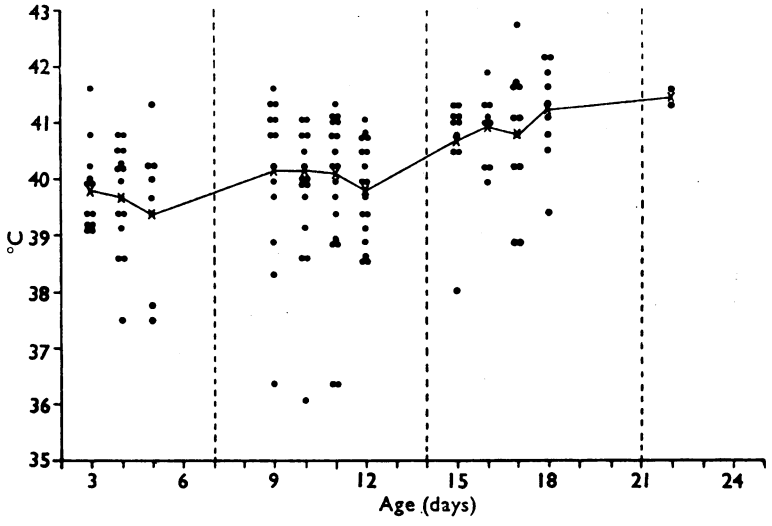

Fig. 2. Scatter diagram of mean surface temperature (°C) in each of 139 chickens aged 3 to 22 days maintained in an oxygen consumption chamber at 31° C. This mean temperature was calculated from 15 min readings over 2 hr, once temperature had stabilized. The mean temperature for all chickens is given by the solid line. Division into weeks given by interrupted vertical lines.

The results shown in Fig. 2 are the means for the 2 hr period after temperature had become steady and are recorded from 139 chickens aged 3 to 22 days in an oxygen consumption chamber at 31° C. "Surface" temperature was recorded since chickens tolerated a thermistor implanted in the mediastinum less well. "Surface" and "core" temperatures differed usually by about 0.5° C and followed each other with fidelity.

The mean temperature increased with age—for example, there was an increase of 1.5° C between the third and seventeenth day. This increase in temperature was accompanied by a decline in oxygen consumption over the same period and under similar circumstances. Presumably the older chickens were able to maintain a higher temperature with smaller heat production, because of either more efficient central mechanisms for temperature control or thermal insulation due to growth of feathers or both.

Effects of catecholamines in 1–23 day chickens

The results differed according to whether young or adult chickens were tested.

Intravenous injection

Effects on temperature. The α-methyl derivatives of adrenaline or noradrenaline given intravenously regularly lowered temperature; adrenaline or noradrenaline were less consistent in this respect. Figure 3 illustrates the effects of α-methyl noradrenaline (10 μ-mole/kg). Core and surface temperatures fell 2° to 3° C within 15 min of the injection, core temperature remaining 0.5° C higher than that of the surface; temperature partially recovered in the ensuing 100 min but fell again later. This inability to regain temperature after injecting α-methyl noradrenaline or α-methyl adrenaline was observed in chickens aged 7 days or less and occasionally in those up to 14 days, although temperature could usually be restored by taking the chicken from the chamber and warming under a lamp.

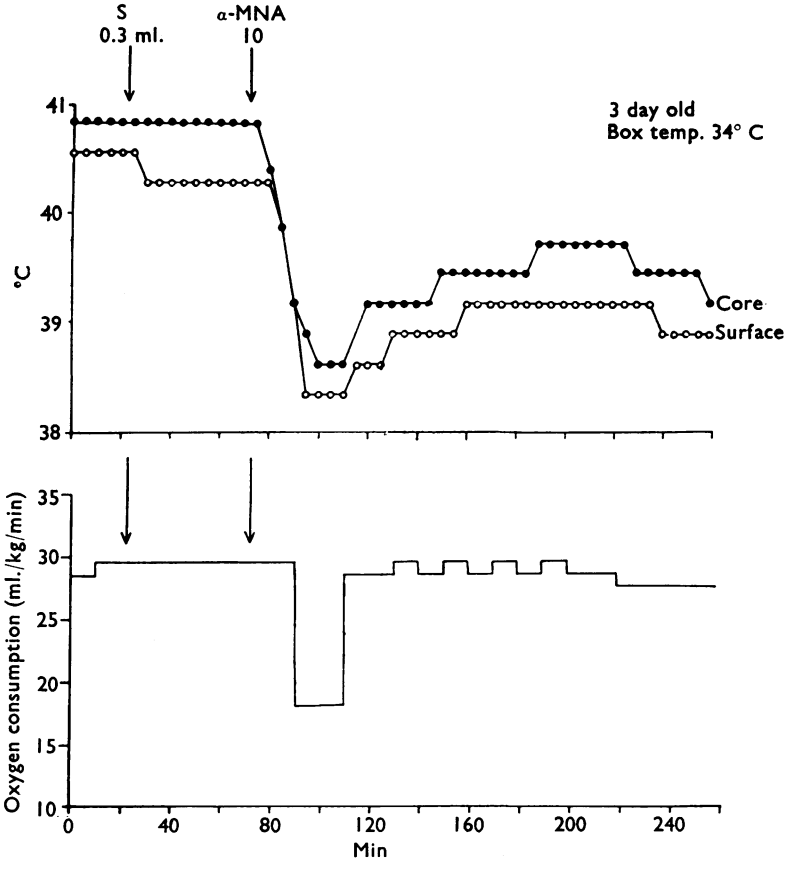

Fig. 3. Graphs of temperature and histograms of oxygen consumption in a 3-day chicken maintained at 34° C. Core (●) and surface (○) temperatures were lowered by α-methyl noradrenaline (αMNA, 10 μ-mole/kg) with little recovery over the ensuing 160 min; oxygen consumption was lowered for 20 min. S=injection of saline.

This suggested that in spite of tests being made in an environment maintained at 31° or 34° C, these amines not only reduced temperature but also produced a tendency to poikilothermia. Until this was realized, a considerable number of chickens with marked (4° C) or protracted (>2 hr) falls of temperature died.

In chickens 10 days or older, even at a lower environmental temperature (20° C, Fig. 4A), a fall of 4° C due to α-methyl noradrenaline was followed by a return to normal temperature. This made it possible to give two doses of α-methyl noradrenaline in the same experiment; the effects were proportional to dose. For example, in a 9-day chicken, core and surface temperature fell 0.6° C following 2.5 μ-mole/kg α-methyl noradrenaline and 2.4° C after 10 μ-mole/kg (60 min later). However, even in these older chickens it was unusual to obtain three-point dose response curves, because of poor temperature recovery from the third dose.

The α-methyl derivative of adrenaline was more potent than that of noradrenaline. For example, 2.5 μ-mole/kg α-methyl adrenaline given to a 16-day chicken evoked a gradual fall in skin temperature of 2° C from a control value of 41.7° C; doses of 5 μ-mole/kg elicited falls of 2° C and 3.1° C in chickens aged 19 and 22 days, with recovery in 50 and 80 min respectively. With 10 μ-mole/kg α-methyl adrenaline given to a 10-day chicken, the core temperature declined 2.8° C over the ensuing 100 min. Since there was no recovery, the chicken was removed from the chamber and warmed but nevertheless died.

Comparatively large doses of adrenaline (0.1 to 1.0 μ-mole/kg) or noradrenaline (0.1 to 2.0 μ-mole/kg) were required to elicit falls in temperature similar to those produced by their α-methyl derivatives. Following the larger doses of adrenaline or noradrenaline and as with their α-methyl derivatives, there was a tendency to poikilothermia in chickens less than 10 days old and temperature did not recover unless they were taken from the chamber and warmed. Adrenaline was two to three times more potent than noradrenaline.

Effects on oxygen consumption. The larger falls in temperature were accompanied by a temporary reduction in oxygen consumption. As shown in Fig. 3 the fall in temperature evoked by α-methyl noradrenaline was associated with a 39% decline in oxygen consumption from 29.5 to 18 ml./kg/min, maximal 18 min after injection and lasting 20 min. Although oxygen consumption usually recovered before that of temperature this was not invariable. For example, a fall of temperature of 3.1° C in an 11-day chicken produced by noradrenaline (2 μ-mole/kg) was maximal at 15 min with recovery at approximately 50 min. Oxygen consumption declined from 24.5 ml./kg/min to 11.7 ml./kg/min by 20 min with recovery at 60 min.

Subcutaneous injection

In young kittens, noradrenaline (400 μg/kg) injected subcutaneously raises temperature and augments oxygen consumption (Moore & Underwood, 1963). Noradrenaline was, therefore, injected subcutaneously in a 15-day chicken to ascertain whether the difference in effects observed between young chickens and kittens depended on the route of injection. The catheter was implanted subcutaneously as described in Methods with the tip overlying the lumbar vertebrae.

Noradrenaline 400 μg/kg (ca. 1.19 μ-mole/kg) given subcutaneously was without effect on temperature. When the dose was increased to 4.76 μ-mole/kg, core and surface temperatures fell 0.25° C, 10 min after injection. Noradrenaline (19.0 μ-mole/kg) lowered core and surface temperatures 1° C, the fall beginning 10 min after injection and becoming maximal at 35 min, with recovery after 180 min.

Intraperitoneal injection

In these experiments surface temperature only was measured. Injections were made via a polyethylene catheter implanted within the peritoneum. Noradrenaline (10 μ-mole/kg) injected into an 11-day chicken lowered temperature 1° C from 41.5° C, the fall commencing 15 min after injection and becoming maximal at 35 min. Temperature recovered 0.5° C 85 min after injection, and then fell again to 40.5° C for the ensuing 75 min when the experiment was ended. The changes in oxygen consumption paralleled those in temperature. With the initial temperature fall, oxygen consumption declined from 16.2 to 12 ml./kg/min, rose with the transitory increase in temperature and fell once more as temperature again declined. In a 12-day chicken, noradrenaline (5 μ-mole/kg intraperitoneally) lowered temperature 0.5° C from 38.5° C and oxygen consumption from 11.4 to 9.2 ml./kg/min with recovery 40 min later. Adrenaline (10 μ-mole/kg) lowered temperature 1.5° C and oxygen consumption from 11.7 to 8.1 ml./kg/min with recovery in 115 min. In a chicken aged 9 days, α-methyl adrenaline (10 μ-mole/kg) reduced temperature 0.25° C and oxygen consumption from 17.6 to 15.2 ml./kg/min for 50 min. A dose of 40 μ-mole/kg reduced temperature 1° C and oxygen consumption from 17.6 to 15.2 ml./kg/min for the subsequent 175 min until the end of the experiment.

Thus with intravenous, subcutaneous or intraperitoneal injection of catecholamines, temperature and oxygen consumption were decreased.

Antagonists at α-receptors for catecholamines

Two chickens were tested. In the first (Fig. 4A) an intravenous dose of α-methyl noradrenaline (10 μ-mole/kg) given to a 13-day chicken at an environmental temperature of 20° C lowered core temperature from 39.1° to 35° C over a period of 40 min with subsequent recovery 200 min after injection. The chicken became deeply asleep with the appearance of paradoxical sleep activity in the electrocorticogram and loss of electromyographic activity. The chicken was then given phenoxybenzamine (100 μ-mole/kg intraperitoneally) and tested again after 3 days (Fig. 4B). On this occasion, 10 μ-mole/kg α-methyl noradrenaline produced a fall of only 1° C with recovery in 120 min and a subsequent intravenous dose of 20 μ-mole/kg was ineffective. The chicken remained alert throughout the experiment, electrocortical and electromyographic activity being unchanged. In a second chicken (10 days old) given phenoxybenzamine (160 μ-mole/kg intraperitoneally 3 days previously) a total of 32.5 μ-mole/kg α-methyl adrenaline injected intravenously and in divided doses lowered rectal temperature 2.5° C, whereas before phenoxybenzamine, a considerably smaller dose (2.5 μ-mole/kg) had elicited a fall of 3° C. To ensure there was no loss of sensitivity to a second dose of α-methyl noradrenaline for the period under test, α-methyl noradrenaline (10 μ-mole/kg) was given to a chicken aged 13 days and next to the same chicken aged 16 days. The fall of core temperature was respectively 2.2° and 2.6° C and of roughly similar duration on the two occasions.

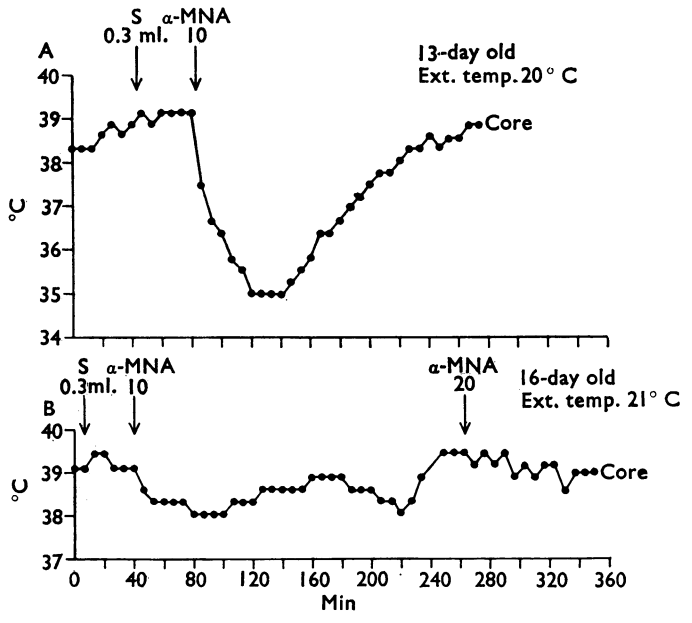

Fig. 4. Graphs of core temperature in a 13-day chicken at room temperature of 20° C. A = fall of temperature following α-methyl noradrenaline (αMNA, 10 μ-mole/kg), with recovery in 200 min. B = same chicken 16 days old and given phenoxybenzamine (100 μ-mole/kg intraperitoneally) 3 days previously. Injections of α-methyl noradrenaline (10 and 20 μ-mole/kg) now produced little temperature change. Saline (S) was without effect in both experiments.

Effects of catecholamines in adult fowls

Four adult fowls were tested at environmental temperatures between 21° and 24.5° C. In the first, noradrenaline (0.1 and 0.4 μ-mole/kg) did not alter core or surface temperatures before or after cocaine (3 μ-mole/kg). In the next, adrenaline in doses of 0.02, 0.1, 0.3 and 0.5 μ-mole/kg raised core and surface temperatures, 0.25° C, both before and after cocaine (10 μ-mole/kg). In the other two fowls, the maximal effect of doses of 10 and 50 μ-mole/kg α-methyl noradrenaline given intravenously was to lower core temperature and raise surface temperature 0.5° C for 30 min.

Other methods of lowering temperature

Tests were next made to ascertain whether the effects obtained on lowering temperature with the catecholamines were similar to these obtained by cooling.

Cooling

One method of cooling was to immerse a chicken up to the neck in water at 22° C for 30 sec. In the experiment of Fig. 5A a 3-day chicken was so immersed for 30 sec and then warmed under a lamp to maintain an air temperature of 30° C surrounding the chicken. Core and surface temperatures fell 7.0° and 6.1° C respectively, reaching a nadir of 33.3° C, 30 min after immersion. In contrast to experiments with α-methyl

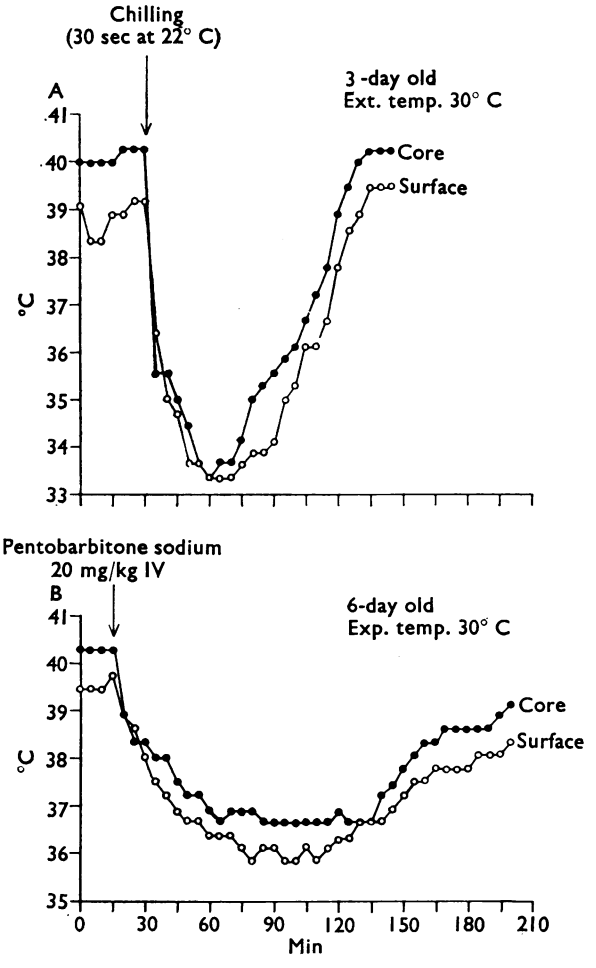

Fig. 5. Graphs of core and surface temperatures. A=fall in temperature with recovery in 105 min following immersion of a 3-day chicken in water at 22° C for 30 sec and then kept in air warmed to 30° C by a lamp. B=same chicken given pentobarbitone (20 mg/kg) 3 days later and kept in air warmed to 30° C. The fall in temperature was less but more prolonged than after immersion in water.

noradrenaline in a 3-day chicken (Fig. 3) and despite a greater fall in temperature, recovery of core and surface temperatures was rapid, being complete 105 min after immersion.

The effects of a longer period of cooling are shown in Fig. 6A. In these tests, a chicken was placed for 2 hr in an oxygen consumption chamber at a temperature of 31° C. Mean oxygen consumption for 9 chickens under these conditions was 33.4 ml./kg/min and mean body temperature 40° C. The chamber and its contained chicken were next immersed in a bath at 16° C and left for 45 min so that thermal equilibrium between bath and chamber would re-establish. Recordings were begun again after the

45 min and, in the ensuing 120 min, mean oxygen consumption for the 9 chickens rose to 50.5 ml./kg/min and mean temperature fell to 37.1° C. The increase in oxygen consumption ranged from 10 to 100% in individual chickens, and in 6 of the 9 the increase was 50% or more. Following chilling, and on returning the chickens to the chamber at 31° C, mean oxygen consumption and temperature returned rapidly to control values. In spite, therefore, of similar falls in temperature with chilling and with catecholamines, the effect on oxygen consumption was quite different.

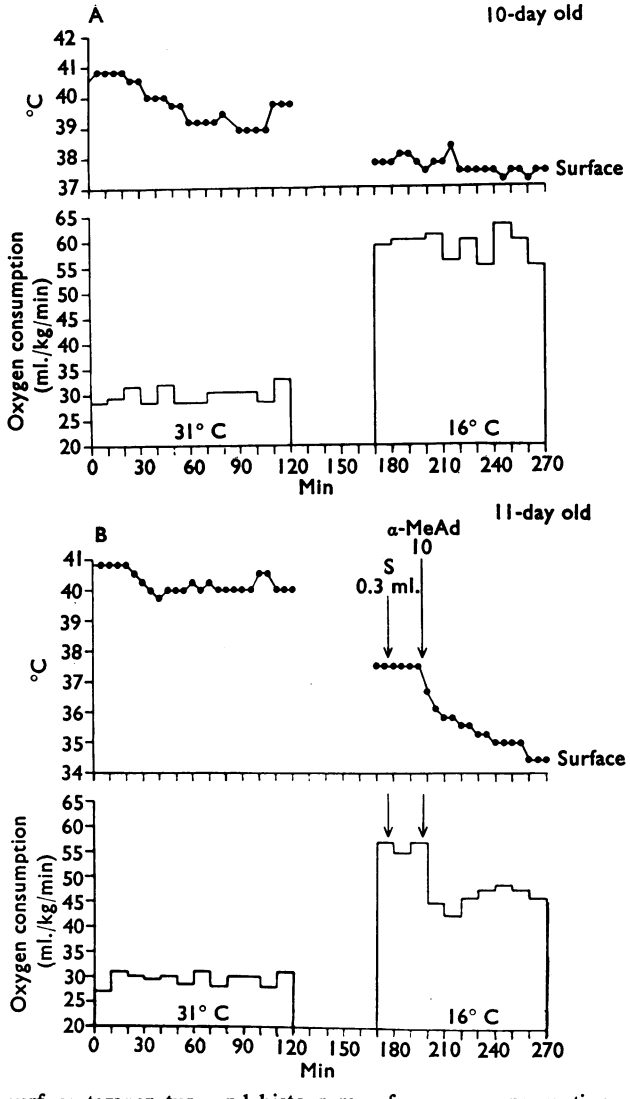

Fig. 6. Graphs of surface temperature and histograms of oxygen consumption. A = 10-day chicken maintained at box temperature of 31° C for 2 hr, followed by cooling at 16° C with fall in temperature and increase in oxygen consumption. B = same chicken tested on subsequent day. Increase in oxygen consumption on cooling at 16° C was reduced by α-methyl adrenaline (αMeAd, 10 μ-mole/kg), and the fall of temperature augmented. Saline (S) was without effect.

The experiments were then repeated in 2 other chickens to determine whether α-methyl adrenaline would antagonize the increase in oxygen consumption produced by cooling. As shown in Fig. 6A mean oxygen consumption in a 10-day chicken rose from 29.9 ml./kg/min at 31° C to 59.1 ml./kg/min at 16° C, with a fall in mean temperature of 2.1° C. This chicken was re-tested the following day (Fig. 6B). Mean oxygen consumption increased from 28.3 ml./kg/min at 31° C to 56.2 ml./kg/min at 16° C. After 28 min, α-methyl adrenaline (10 μ-mole/kg) was injected and mean oxygen consumption subsequently fell to 46.1 ml./kg/min. The increase in oxygen consumption during chilling but following α-methyl adrenaline was significantly smaller than in the control ($CR = 8.79$, $P < 0.001$), despite a significantly greater ($CR = 5.68$, $P < 0.001$) fall in mean temperature (4.9° C). A smaller depressant effect on oxygen consumption during chilling was obtained with α-methyl adrenaline (5 μ-mole/kg). The depressant effects of α-methyl adrenaline on oxygen consumption may have been superimposed on a dwindling response to cooling due to habituation during the second exposure. That this was not so is evident from Table 1, in which data from 2 chickens tested on consecutive days is shown. The response to cooling on the second occasion was as large as the first.

TABLE 1

MEAN AND STANDARD DEVIATIONS OF OXYGEN CONSUMPTION AND TEMPERATURE IN 4 CHICKENS EXPOSED FOR 120 MIN TO A TEMPERATURE OF 31° C AND THEN OF 16° C ON TWO CONSECUTIVE DAYS

Chickens (no.)	Age (days)	Mean O_2 consumption (ml./kg/min) 31° C	16° C	Mean temperature (°C) 31° C	16° C
2	4	21·8±7·4	56·3±4·6	40·6±2·1	36·3±1·3
	5	21·8±3·5	57·2±2·9	40·5±1·6	36·4±2·4
2	10	19·9±4·4	43·3±4·2	40·3±2·3	35·0±2·0
	11	21·7±6·7	44·1±7·8	39·6±1·5	35·4±2·4

The difference between the effects of cooling and of the catecholamines on oxygen consumption suggested that the central nervous system was depressed by the catecholamines and unresponsive to hypothermia. To establish this more firmly, the effects were compared with those of pentobarbitone given in doses to produce sleep but not anaesthesia.

Pentobarbitone

Oxygen consumption was little affected by doses of pentobarbitone that produced substantial falls in temperature. Pentobarbitone (20 mg/kg in two doses) given to an 11-day chicken at 31° C (Fig. 7A), reduced oxygen consumption from an average of 29 ml./kg/min for the control 60 min to between 20 and 23.7 ml./kg/min over the following 200 min. This reduction was accompanied by a decrease in surface temperature from 40.3° to 37.5° C. Temperature and oxygen consumption had both recovered 240 min after the injection and rose still further over the subsequent 80 min. Similar results were obtained in a second chicken.

As with the catecholamines a fall in surface temperature was paralleled by that in core temperature. This is shown in Fig. 5B. In the 70 min following pentobarbitone (20 mg/kg), core and surface temperatures fell 3° and 4° C and the 6-day chicken became drowsy and lay on its side. Some 120 min after pentobarbitone, the chicken was again able to stand, and by 200 min core and surface temperatures had substantially recovered.

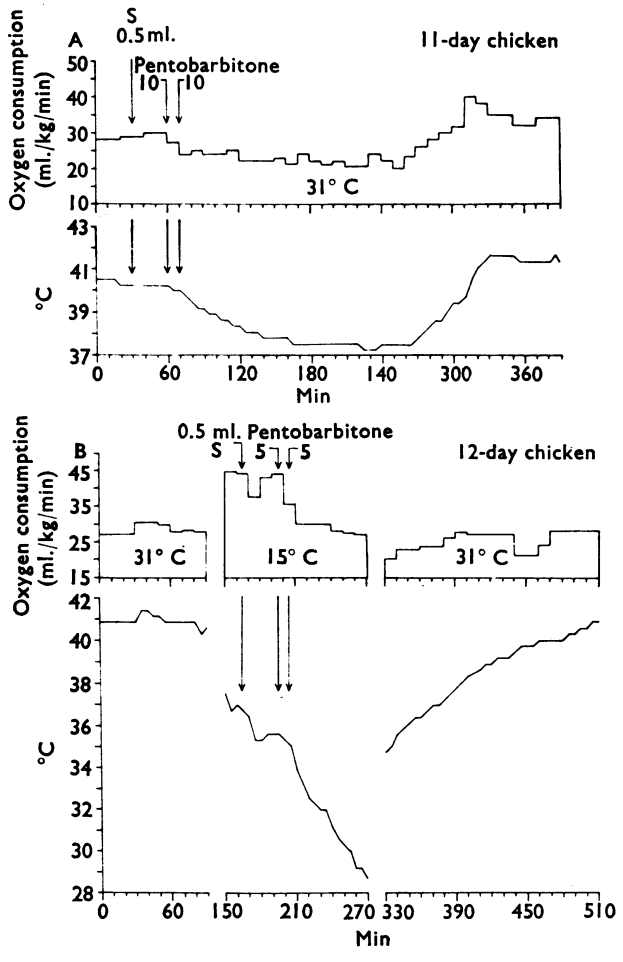

Fig. 7. Graphs of surface temperature and histograms of oxygen consumption in two chickens. A = 11-day chick given pentobarbitone (20 mg/kg). Temperature and oxygen consumption were lowered, but with recovery 240 min after injection when both temperature and oxygen consumption rose above pre-injection values. B = 12-day chicken kept initially for 90 min at 31° C. Cooling at 15° C produced a rise in oxygen consumption. This was abolished by pentobarbitone (10 mg/kg), which also enhanced the fall in temperature. Temperature restored by transfer to chamber at 31° C. S = saline.

The effects of pentobarbitone (10 mg/kg in two doses) and chilling at 15° C were next tested in a 12-day chicken (Fig. 7B). Mean oxygen consumption increased from 28.2 ml./kg/min at 31° C to 42.1 ml./kg/min at 16° C but, after pentobarbitone, this was promptly reduced to 31.3 ml./kg/min. Temperature fell dramatically from a control of 37.5 to 28.6° C. On transferring the chicken to the chamber at 31° C, temperature rose again. The chicken was still drowsy at the end of the experiment but was roused by handling.

Electromyographic activity

With the α-methyl derivative of adrenaline or noradrenaline given intravenously in the doses described hitherto, electromyographic activity was reduced from an amplitude of 20–40 μV to that of 10–20 μV. Potentials due to head movements were abolished. The reduction in electromyographic activity was associated with sleep. However, once the fall in temperature reached its nadir, electromyographic potentials were increased, concomitantly with the onset of shivering.

Electromyographic activity was considerably augmented by cooling and persisted until the temperature was restored to control values. The effects of α-methyl noradrenaline were substantially diminished under these circumstances. A 12-day chicken was cooled in water at 22° C for 30 sec. Core temperature fell from 41.9° to 35° C and electromyographic activity increased from an amplitude of 10 to 100 μV with superimposed potentials of 300 μV due to shivering. α-Methyl noradrenaline (20 μ-mole/kg) reduced the amplitude to 20 μV for 4 min only.

Effects of tryptamines

Intravenous injection

The effects of α-methyltryptamine (10 μ-mole/kg) in a 12-day chick are shown in Fig. 8. Core temperature was raised 1.1° C and oxygen consumption increased 45% from 20 to 29 ml./kg/min, the effects abating after 120 min. Surface temperature was similarly

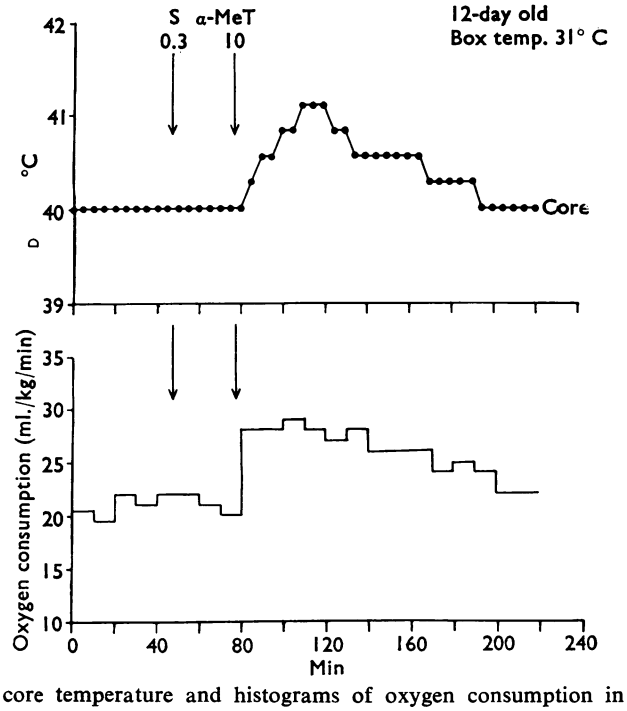

Fig. 8. Graphs of core temperature and histograms of oxygen consumption in a 12-day chicken. α-Methyltryptamine (10 μ-mole/kg) evoked an immediate rise in temperature and oxygen consumption. S=saline.

increased. The rise in oxygen consumption occurred immediately and persisted for as long as the rise in temperature. Similar effects were obtained in 2 other chickens. The increases in temperature and oxygen consumption produced by α-methyltryptamine were abolished by methysergide (0.1 μ-mole/kg).

Although tryptamine by itself was ineffective on temperature and oxygen consumption, after pretreatment with an amine oxidase inhibitor (mebanazine, 100 μ-mole/kg 160 min previously), tryptamine (5 μ-mole/kg, Fig. 9, 1st day) had similar effects to α-methyl tryptamine and raised core temperature in a 15-day chick from 41.9 to 43.2° C.

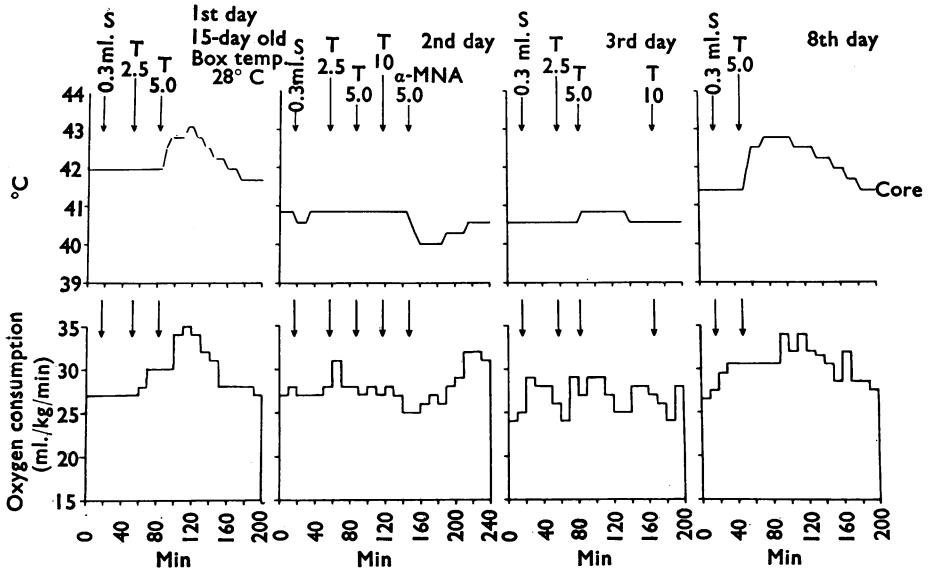

Fig. 9. Graphs of core temperature and histograms of oxygen consumption in the same chicken tested on 4 days. Chicken 15 days old on first test day. Mebanazine (100 μ-mole/kg) given on each test day 160 min before first dose of tryptamine. Injection of mebanazine not shown in Figure. *First day.* Rise in temperature produced by tryptamine (5 μ-mole/kg), increase of oxygen consumption with tryptamine, 2.5 and 5 μ-mole/kg. *Second and third days.* Same chicken and given mebanazine as on first day. Tryptamine up to 10 μ-mole/kg was without effect, although α-methyl noradrenaline (αMNA 5 μ-mole/kg) lowered temperature. *Eighth day.* Same chicken rested for 4 days and given mebanazine as on first day. Tryptamine now raised temperature and oxygen consumption. S = saline.

The rise in temperature reached its maximum after 35 min and returned to control values 90 min after injection. A previous dose of tryptamine (2.5 μ-mole/kg), even though ineffective on temperature, increased oxygen consumption from 25.4 to 30.0 ml./kg/min. Following the 5μ-mole/kg dose, oxygen consumption increased further to 35.0 ml./kg/min. The peak in oxygen consumption coincided with that in temperature and the decline from the peaks of both paralleled one another. On the ensuing 2 days this chicken was injected with mebanazine (100 μ-mole/kg) 160 min before the first dose of tryptamine. Tryptamine in doses of 2.5, 5.0 and 10 μ-mole/kg was now (2nd and 3rd day in Figure) without effect on temperature and oxygen consumption, although temperature was lowered by α-methyl noradrenaline (5 μ-mole/kg), suggesting tachyphylaxis had

developed to tryptamine. When the chicken was re-tested 4 days later and 160 min after mebanazine (100 μ-mole/kg), tryptamine now raised core temperature 1.8° C and increased oxygen consumption (8th day in Figure). Tachyphylaxis to repeated doses of tryptamine was also observed in another chicken.

Intraperitoneal injection

Larger doses of tryptamine tended to lower temperature despite raised oxygen consumption. This is shown in Fig. 10, for a 15-day chicken. Tryptamine (20 μ-mole/kg), given intraperitoneally, 160 min after mebanazine (150 μ-mole/kg) produced a brief fall followed within 30 min by a rise in oxygen consumption from 29 to 38.5 ml./kg/min. Oxygen consumption subsequently declined from this peak, but remained higher than pre-injection values at or about 30.5 ml./kg/min for the rest of the experiment. Temperature rose 0.3° C from 40.5° C accompanying the peak increase in oxygen consumption but then declined to 38.9° C and subsequently remained low.

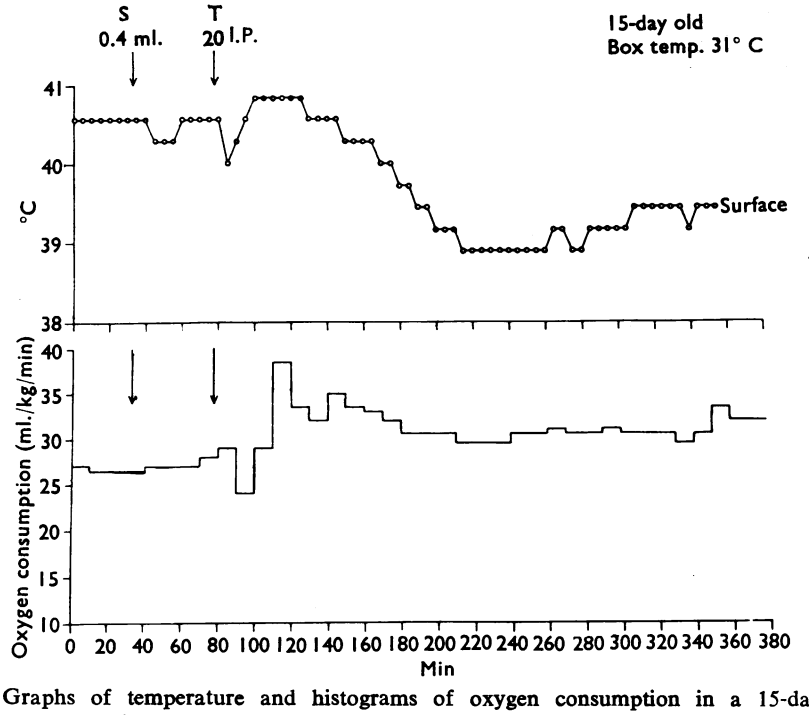

Fig. 10. Graphs of temperature and histograms of oxygen consumption in a 15-day chicken. Oxygen consumption was increased, but temperature after a small rise was lowered by trytamine 20 μ-mole/kg) injected intraperitoneally 160 min after mebanazine (150 μ-mole/kg). S=saline.

Amphetamine-like amines

Dexamphetamine. Tests were made in 3 young and 3 adult chickens. Doses of 5 and 10 μ-mole/kg were given and repeated to a total of 30 μ-mole/kg without any significant change in temperature or oxygen consumption. The adult fowls were tested in the open laboratory and these doses, although ineffective on temperature, evoked pecking, vocalization and postural effects.

Because of the lack of effect of dexamphetamine, two further tests were made. In the first, a 10- and a 12-day chick were maintained at an environmental temperature of 35° C. Dexamphetamine (10 and 20 μ-mole/kg) had no effect on temperature and oxygen consumption. In the second, dexamphetamine was injected after pretreating 2 adult fowls with mebanazine (100 μ-mole/kg 100 min previously). In one, dexamphetamine (10 μ-mole/kg) increased core and surface temperatures 2° C. The temperatures rose immediately after injection from 40.5° C to a peak 45 min later of 42.5° C, which was sustained for 30 min when temperature was restored to pre-injection values by methysergide, 0.1 μ-mole/kg) a specific tryptamine antagonist (Doepfner & Cerletti, 1958). In the other fowl, dexamphetamine (5 and 10 μ-mole/kg) had no effect on temperature but a rise of 2.1° C followed a dose of 20 μ-mole/kg. This was sustained for 120 min when it was abolished by methysergide (1 μ-mole/kg).

β-Phenethylamine. Doses of 5, 10 and 20 μ-mole/kg were ineffective on temperature and oxygen consumption in two chickens pretreated with mebanazine (100 μ-mole/kg 90 min previously).

Tuaminoheptane. Doses of 100 and 200 μ-mole/kg in an 11-day and 200 and 300 μ-mole/kg in a 12-day chick were ineffective on temperature, but with the larger dose in each case mean oxygen consumption rose from 25.5 to 32.5 ml./kg/min and from 30.7 to 37.1 ml./kg/min respectively.

1,2,3,4 β-tetrahydronaphthylamine. β-Tetrahydrotraphythylamine was tested in 5 chickens (5, 10, 12, 12 and 17 days). Doses of 50 and 60 μ-mole/kg even after pretreating 2 of the chickens with mebanazine (100 μ-mole/kg 90 min previously) were virtually ineffective. In 3 chicks there was a rise, and in 2 a fall in temperature of less than 1° C. Oxygen consumption was correspondingly little changed, with a maximum increase or decrease of less than 10%.

Electromyographic activity

With the tryptamines and amphetamine-like drugs given intravenously in the doses described hitherto, electromyographic activity was increased from an amplitude of 20 to 40 μV to 40 to 90 μV. Potentials due to head-movements were also considerably augmented.

Postural changes due to drugs, to cooling and to warming

Postural changes produced by drugs had implications with regard to temperature control. The following tests were made on 4 9-day chickens, and rectal temperature measured. As shown in Fig. 11B, following (−)-α-methyl noradrenaline (40 μ-mole/kg i.p.), the chicken went to sleep standing with lowered wings applied closely to the trunk. Identical postural changes were observed on cooling another chicken in air from 41.7° to 36.7° C (Fig. 11D).

The similarities between the effects of α-methyltryptamine and of warming were also striking. Following (±)-α-methyltryptamine (30 μ-mole/kg intraperitoneally), tachypnoea developed, the wings were extended horizontally away from the trunk (Fig. 11F), and the chicken crouched with its tail elevated (Fig. 11G). On warming another chicken in air

so that its rectal temperature rose from 41.6° to 43.7° C, panting developed, its wings spread horizontally away from the trunk (Fig. 11 I), and it crouched in a similar way to that observed after α-methyltryptamine (Fig. 11J).

The postural changes evoked by α-methyl noradrenaline in young chickens were not observed in adult fowls; in contrast, those produced by α-methyltryptamine occurred in young and adult fowls.

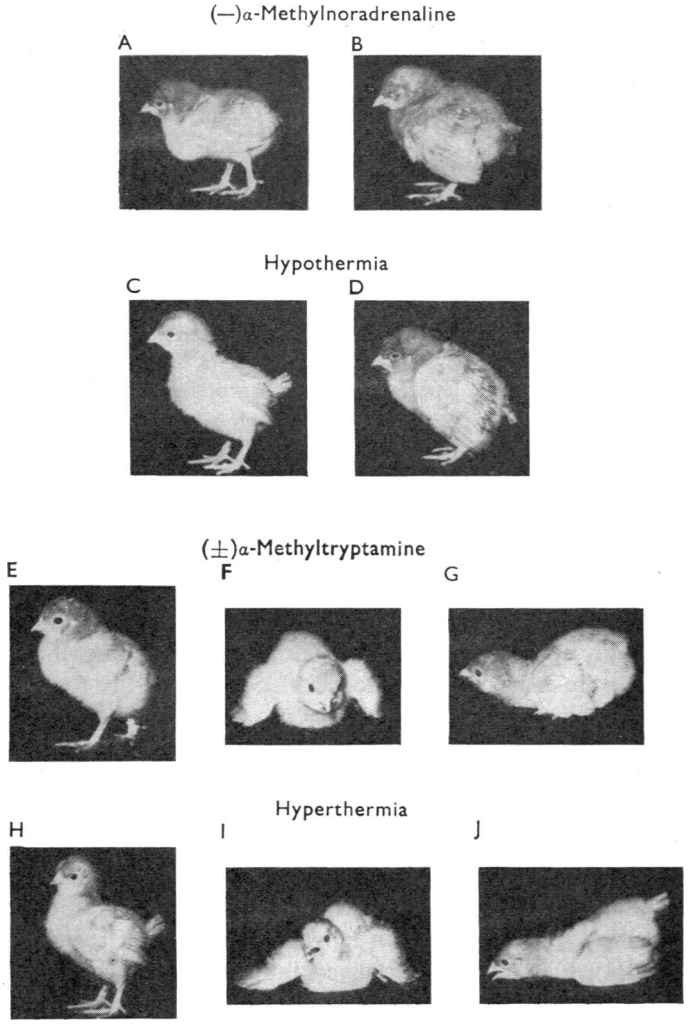

Fig. 11. Postural changes produced in 4 9-day-old chickens by drugs and by altering temperature. A, C, E, H=controls. B=chicken asleep after α-methyl noradrenaline (40 μ-mole/kg intraperitoneally). The wings are lowered and applied closely to the trunk. D=chicken cooled in air with fall of rectal temperature from 41.7 to 36.7° C. Chicken is alert but crouching and with lowered wings as after α-methyl noradrenaline. F, G=chicken alert with wings extended away from the trunk and crouching with tail elevated following (±)-α-methyltryptamine (30 μ-mole/kg intraperitoneally). I, J=similar changes to these produced by α-methyltryptamine but evoked by warming a chicken with a lamp, the rectal temperature rising from 41.6 to 43.7° C.

DISCUSSION

Between hatching and the 10th day of life, the rectal temperature rises 2° C ; thereafter it remains constant (Lamoreux & Hutt, 1939 ; Randall, 1949). A similar increase of core and surface temperatures measured by implanted thermistors as chickens matured was found in the present study. The rise in body temperature as the chicken matured was accompanied by a fall in oxygen consumption. Oxygen consumption varied between 35 to 38 ml./kg/min in 8- to 16-day chickens maintained at 31° C and increased progressively with decreased external temperature.

Prolonged changes in temperature and oxygen consumption were brought about by drugs and by short periods of cooling. The catecholamines adrenaline, noradrenaline and the α-methyl derivatives given intravenously lowered core and surface temperatures. These amines raise blood pressure in chickens (Dewhurst & Marley, 1965b) and the associated vasoconstriction would hinder heat loss. The effects of the α-methyl derivatives of adrenaline and noradrenaline were the most consistent, and were dose-dependent. Chickens aged 7 days or less, and occasionally those up to 14 days, had difficulty in restoring temperature lowered by catecholamines, suggesting that the amines not only reduced temperature but produced a tendency to poikilothermia. This contrasted with the effects of brief immersion in water at 22° C, which lowered temperature further but from which recovery was rapid. Heat loss is greater in water than in air because of conduction of body heat into the fluid, whereas in air the insulating effect of down or feathers remains operative (Sturkie, 1954b). The findings suggest that the profound effects on temperature of the catecholamines were due to depression of heat production rather than to increased heat loss. The fall in temperature was accompanied by a decrease in oxygen consumption which was neither so marked nor so long-lasting as the effects on temperature.

The fall in oxygen consumption also favoured decreased heat production, although the subsequent normal oxygen consumption with lowered temperature indicated that increased heat loss was probably complicating the situation. During the maximum fall in temperature, the chickens were asleep. Electrocortical activity at this time was of the large amplitude slow frequency activity found during physiological sleep (Key & Marley, 1962), although in 2 chickens, paradoxical sleep activity was observed. Similar effects on temperature and oxygen consumption were obtained with soporific doses of pentobarbitone. A striking feature with the catecholamines and pentobarbitone was the rapidity and similar extent of fall in core and surface temperature even with 3-week chicks indicating inadequate mechanisms for preferentially maintaining core temperature. Since our preliminary communication (Allen & Marley, 1966), reduction by adrenaline of temperature and oxygen consumption in young chicks was reported by Ruckebusch, Laplace & Grivel (1966) but the doses given intravenously were large (17 μ-mole/kg). The young chicken differs from the newborn kitten and rat in which noradrenaline has thermogenic properties (Moore & Underwood, 1963).

The response to cooling by lowering air temperature to 16° C differed from that in which temperature was lowered to a similar extent by catecholamines or by pentobarbitone, since oxygen consumption was increased. On recovery from chilling, temperature and oxygen consumption returned to control values. In contrast, after hypothermia with pentobarbitone, temperature and oxygen consumption were raised. A raised temperature on recovery from pentobarbitone anaesthesia has been observed

in cats (Feldberg & Myers, 1964b). The raised oxygen consumption during chilling was significantly reduced by catecholamines or by pentobarbitone with associated non-lethal falls in temperature of up to 9° C.

The hypothermic effects of α-methyl derivatives of adrenaline or noradrenaline were presumably mediated through α-receptors for catecholamines, since they were prevented by pretreatment with phenoxbenzamine. That hypothermia induced by catecholamines but not that induced by cooling was accompanied by sleep suggested an action on the central nervous system rather than one in the periphery. This was supported by the rapid onset of hypothermia, its relatively long duration and the similarity of effects obtained with pentobarbitone. Strong evidence for a central action was the similar hypothermic and soporific effects of α-methyl noradrenaline perfused into the lateral hypothalamic area in one-fortieth the intravenous dose (Marley & Stephenson, unpublished). The lack of effect of catecholamines on temperature in adult fowls accords with their lack of soporific effects and contrasts with their hypothermic and soporific actions in young chickens. The results were compatible with the amines penetrating to the brain in young but not adult chickens.

The posture produced by soporific doses of catecholamines and pentobarbitone or by cooling in which the head droops and wings are lowered and applied closely to the trunk, the head is tucked beneath a wing or the chick squats, all serve to hinder heat loss. In domestic fowls, heat loss while standing is 40 to 50% greater than during sitting, and tucking the head beneath a wing reduces heat dissipation by 12% (Deighton & Hutchinson, 1940). Thus, although heat production appears to be depressed by soporific doses of catecholamines or pentobarbitone, heat conservation mechanisms were maintained. Heat production as evidenced by shivering was much depressed in contrast to the cooling experiments in which shivering was marked.

Temperature and oxygen consumption were raised by α-methyltryptamine or after pretreating chickens with an amine oxidase inhibitor mebanazine, by tryptamine or dexamphetamine. The effects were antagonized or prevented by methysergide, a specific tryptamine antagonist, implying an action on tryptamine receptors in the brain. Whereas temperature was more sensitive than oxygen consumption to the effects of catecholamines and pentobarbitone, the reverse applied for tryptamines and dexamphetamine.

The postural changes produced by the excitant amines have implications with regard to temperature control, since the wing elevation and tachypnoea were also obtained on warming and presumably assist heat loss. The elevated wings increased surface area and exposed the brachial vessels on the ventral aspects of the wings. The postural changes were, however, mediated through centres anatomically separate from those controlling temperature since they were obtained in chickens with a transection immediately posterior to the hypothalamus (Marley & Stephenson, unpublished).

The excitant amines all increased electromyographic activity with presumably augumented heat production. That the tryptamines had calorigenic actions may simply mean that heat production exceeded heat loss, whereas with the other excitant amines heat loss kept pace with heat production and so there was no increase in temperature and oxygen consumption. Lowered temperature after large doses of tryptamine despite increased oxygen consumption could also be attributed to heat loss exceeding heat

production. In this case not only would the extreme postural changes favour heat loss but by rendering the chickens immobile and incapable of movement, would expedite it.

Although birds are known to be resistant to pyrexic agents (Sollman, 1957), it is difficult to account for the lack of calorigenic effect of cyclopentamine, tuaminoheptane and β-phenethylamine given either alone or in chickens pretreated with an amine oxidase inhibitor, compounds which have otherwise identical central effects to α-methyltryptamine. That dexamphetamine was ineffective on temperature and oxygen consumption unless chickens were pretreated with an amine oxidase inhibitor suggests that the enzyme inhibitor was affecting other enzymes, including those responsible for metabolizing amphetamine (see Pletscher, 1966).

From previous studies with young chickens it appeared that the central excitant sympathomimetic amines such as amphetamine, cyclopentamine, tuaminoheptane and α-methyltryptamine were a homogeneous group despite their variety of chemical structure (Dewhurst & Marley, 1965b). However, the present experiments indicate that amines have additional sites of action because of their effects on temperature and oxygen consumption. Similar conclusions were derived from operant experiments utilizing key-pecking in chickens in which dexamphetamine and α-methyltryptamine were found to have different effects. Thus with doses that were otherwise equiactive, and provided the schedule generated a low control rate of pecking, pecking was increased by dexamphetamine but reduced or suppressed by α-methyltryptamine; the effect of dexamphetamine was prevented by phenoxybenzamine but that of α-methyltryptamine by methysergide (Marley & Morse, 1967).

The idea that drugs such as the sympathomimetic amines produce their central effects through some crucial integrating area in the brain such as the reticular formation may therefore require modification to include higher centres such as the hypothalamus. The importance of a hypothalamic site of action for noradrenaline and 5-hydroxytryptamine has been shown by Feldberg & Myers (1965), who made the important suggestion that release of these amines within the hypothalamus regulates temperature.

SUMMARY

1. Oxygen consumption and temperature have been recorded in young and adult chickens. Core and surface temperatures increased about 2° C between hatching and 22-days; this was accompanied by a decline in oxygen consumption of about 10%. Oxygen consumption increased as environmental temperature was lowered.

2. Drugs were injected without interfering with continuous recording of temperature or oxygen consumption.

3. Temperature and oxygen consumption were decreased by noradrenaline, adrenaline and their α-methyl derivatives in chickens up to 23 days but not in adult fowls. In addition to lowering temperature, the amines produced a tendency to poikilothermia in chickens 7 days old or less. These hypothermic effects were accompanied by behavioural and electrocortical sleep and were prevented by pretreatment with phenoxybenzamine. Similar effects on temperature and oxygen consumption were obtained with soporific doses of pentobarbitone.

4. Cooling chickens in air at 16° C lowered temperature but increased oxygen consumption on average 50%. This effect of cooling on oxygen consumption was diminished by soporific doses of catecholamines or pentobarbitone although the temperature fall was enhanced.

5. Temperature and oxygen consumption were increased by α-methyltryptamine; dexamphetamine and tryptamine had similar effects in chicks pretreated with an amine oxidase inhibitor, mebanazine. These effects were antagonized or prevented by methysergide, a tryptamine antagonist. Large doses of tryptamine given after an amine oxidase inhibitor increased oxygen consumption but paradoxically lowered temperature.

6. Amines such as cyclopentamine, tuaminoheptane and dexamphetamine with similar excitant effect to α-methyltryptamine, nevertheless lacked calorigenic actions. β-phenethylamine, cyclopentamine and tuaminoheptane were also ineffective after pretreating chickens with mebanazine.

7. Postural changes produced by catecholamines in young chickens were similar to those produced by cooling in air or fluid. Postural changes evoked in young or adult chickens by tryptamines and dexamphetamine resembled those due to warming in air.

One of us (EM) gratefully acknowledges support from the Medical Research Council. Our thanks are due to Miss P. Notermans for typing the manuscript and to Mrs. J. A. Stein and Miss C. Wilson for technical assistance. We are indebted to Eli Lilly for (±)-tuaminoheptane, Hoescht Pharmaceuticals for (−)-α-methyl noradrenaline, and (−)-α-methyl adrenaline, to I.C.I. for halothane and mebanazine, to Parke Davis & Co. for (+)-α-methyltryptamine; Smith Kline & French Laboratories for dexamphetamine and phenoxybenzamine; Sterling-Winthrop for (−)-noradrenaline, and Professor J. R. Vane for (±)-α-methyltryptamine.

REFERENCES

ALLEN, D. J. & MARLEY, E. (1966). Actions of amines on temperature in the chicken. *J. Physiol., Lond,* **183**, 61–62P.

BURN, J. H. & RAND, M. J. (1958). The action of sympathomimetic amines in animals treated with reserpine. *J. Physiol., Lond.*, **144**, 314–336.

DEIGHTON, T. & HUTCHINSON, J. C. D. (1940). Studies on the metabolism of fowls. *J. agric. Sci.*, **30**, 463–484.

DEWHURST, W. G. & MARLEY, E. (1965a). The effects of α-methyl derivatives of noradrenaline, phenylethylamine and tryptamine on the central nervous system of the chicken. *Br. J. Pharmac. Chemother.*, **25**, 682–704.

DEWHURST, W. G. & MARLEY, E. (1965b). Action of sympathomimetic and allied amines on the central nervous system of the chicken. *Br. J. Pharmac. Chemother.*, **25**, 705–727.

DOEPFNER, W. & CERLETTI, A. (1958). Comparison of lysergic acid derivatives and antihistamines as inhibitors of the edema provided in the rat's paw by serotonin. *Int. Archs Allergy appl. Immun.*, **12**, 89–97.

FELDBERG, W. & MYERS, R. D. (1963). A new concept of temperature regulation by amines in the hypothalamus. *Nature, Lond.*, **200**, 1325.

FELDBERG, W. & MYERS, R. D. (1964a). Effects on temperature of amines injected into the cerebral ventricles. A new concept of temperature regulation. *J. Physiol., Lond.*, **173**, 226–237.

FELDBERG, W. & MYERS, R. D. (1964b). Temperature changes produced by amines injected into the cerebral ventricles during anaesthesia. *J. Physiol., Lond.*, **175**, 464–478.

FELDBERG, W. & MYERS, R. D. (1965). Changes in temperature produced by micro-injections of amines into the anterior hypothalamus of cats. *J. Physiol., Lond,*, **177**, 239–245.

FLECKENSTEIN, A. & BURN, J. H. (1953). The effect of denervation on the action of sympathomimetic amines on the nictitating membrane. *Br. J. Pharmac. Chemother.*, **8**, 69–78.

KEY, B. J. & MARLEY, E. (1962). The effect of the sympathomimetic amines on behaviour and electrocortical activity of the chicken. *Electroen. Neurophysiol.*, **14**, 90–105.

LAMOREUX, W. F. & HUTT, F. B. (1939). Variability of body temperature in the normal chick. *Poultry Sci.*, **18**, 70–75.

MARLEY, E. (1962). Action of some sympathomimetic amines on the cat's iris, *in situ* or isolated. *J. Physiol., Lond.*, **162**, 193–211.

MARLEY, E. & MORSE, W. H. (1967). Effects of α-methyl derivatives of noradrenaline, phenethylamine and tryptamine on operant conditioning in chickens. *Br. J. Pharmac. Chemother.*, In press.

MARLEY, E. & PAYNE, J. P. (1964). Halothane anaesthesia in the fowl. In *Small Animal Anaesthesia*, pp. 127–134. Pergamon Press, Oxford.

MAXWELL, R. A., POVALSKI, H. & PLUMMER, A. J. (1959). A differential effect of reserpine on pressor amine activity and its relationship to other agents producing this effect. *J. Pharmac. exp. Ther.*, **125**, 178–183.

MOORE, R. E. & UNDERWOOD, M. C. (1963). The thermogenic effects of noradrenaline in new-born and infant kittens and other small animals. A possible hormonal mechanism in the control of heat production. *J. Physiol., Lond.*, **168**, 290–317.

PLETSCHER, A. (1966). Monoamine oxidase inhibitors. *Pharmac. Rev.*, **18**, 121–129.

RANDALL, W. C. (1949). Factors influencing the temperature regulation of birds. *Am. J. Physiol.*, **139**, 56–63.

RICHARDS, A. N. & COLLISON, L. W. (1928). An apparatus for the continuous recording of the oxygen consumption of small animals. *J. Physiol., Lond.*, **66**, 299–306.

ROBINSON, K. W. & LEE, D. H. K. (1947). The effect of the nutritional plane upon the reactions of animals to heat. *J. Anim. Sci.*, **6**, 182.

RUCKEBUSCH, Y., LAPLACE, J. P. & GRIVEL, M. L. (1966). Variations de l'activité médicamenteuse en fonction de l'âge: étude chez le Poussin. *Thérapie*, **21**, 1113–1120.

SOLLMANN, T. (1957). *A Manual of Pharmacology*, 8th ed., p. 691. Saunders, Philadelphia.

STURKIE, P. D. (1954a). *Avian Physiology*, p. 145. Comstock, New York.

STURKIE, P. D. (1954b). *Avian Physiology*, p. 121. Comstock, New York.

TRENDELENBURG, U. (1963). Supersensitivity and subsensitivity to sympathomimetic amines. *Pharmac. Rev.*, **15**, 225–276.

VANE, J. R. (1960). The actions of sympathomimetic amines on tryptamine receptors. In *Ciba Foundation Symposium on Adrenergic Mechanism*, ed. VANE, J. R., WOLSTENHOLME, G. E. W. & O'CONNOR, M., pp. 356–372. Churchill, London.