STUDY OF BIOGENIC AMINES ON THERMOREGULATORY MECHANISM AND VASCULAR RESPONSES IN FOWL

BY

Kameshwar Prasad Yadava

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JABALPUR (M. P.)

In the memory of my

late mother.

Prof.A.Ahmad,
B.V.Sc.& A.H.,M.S.,Ph.D.

Department of Pharmacology,
College of Veterinary Science & A.H.
Jabalpur (M.P.)

CERTIFICATE

Certified that the thesis entitled " STUDY OF BIOGENIC AMINES ON THERMOREGULATORY MECHANISM AND VASCULAR RESPONSES IN FOWL" incorporates the results of the work carried out by Dr.K.P.Yadava, B.V.Sc. & A.H. (Hons.) under my supervision and guidance during the academic year 1969-70.

Dated, 26 Oct. 1970.

(Allauddin Ahmad)
University Professor & Head.

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CHAPTER I

INTRODUCTION

INTRODUCTION

The evidences that hypothalamus is the seat of the thermostatic control of body temperature in birds as in mammals have been reported by several workers (Rogers & Lackey, 1923; Rogers, 1923 & 1928; Randall, 1943). According to Feldberg (1968) the statement that body temperature is under the influence of hypothalamus poses two problems.(1) What is the mechanism by which the hypothalamus maintains a constant body temperature in homeotherms? (2) What goes on in this part of the brain to bring about changes in body temperature? Our present work is concerned with second problem, but its solution will clearly influence our ideas about the first.

Feldberg & Myers (1963, 1964a) based on experiments in cats proposed the concept that the thermoregulation is mediated through the release of three biogenic amines i.e. 5-hydroxytryptamine (5-HT), norepinephrine (NE) and epinephrine (EN). Tentatively this idea was also suggested earlier by Brodle & Shore (1957) and von Euler (1961), based on relatively meagre evidence available at that time. Application of this new theory of thermoregulation in birds will imply that these three biogenic amines like mammalian species must be present in the avian hypothalamus as well, and

they are present in higher concentrations in this part of diencephalon as reported by Pscheidt & Haber (1965), Jurio & Vogt (1967) and Aprison & Takahashi (1967). Besides these three biogenic amines and their corresponding acid metabolites (homovanillic acid and 5-hydroxyindolacetic acid), some of the important enzymes such as 'L-amino-acid decarboxydase' and 'monoamine oxidase' (MAO), implicated in their synthesis and inactivation have been also reported to occur in the avian thalamus and hypothalamus and their presence is, perhaps, a stronger evidence for the physiological function of these amines than the mere presence of active amines themselves.

Use of fluorescent histochemical technique has recently revealed the existence of monoaminergic (serotonergic and catecholaminergic) pathway in mammalian as well as in avian brain (Carlsson et al, 1962; Dahlstrom & Fuxe, 1964; Anden et al, 1965 and Jurio & Vogt, 1967) and these three biogenic amines (5-HT and NE & EN) appear to be the central synaptic transmitter of monoaminergic neurones. Based on such studies these three amines have been seen to be located mainly not in the nerve cells but in the nerve fibres and nerve endings. This recalls the location of acetylcholine in the sympathetic ganglia. Here, too, acetylcholine

is mainly not located in the ganglion cells but in the preganglionic cholinergic nerve fibres and endings. In the same way as the high acetylcholine content in the sympathetic ganglia results from the cholinergic neurones which make synaptic connections with ganglion cells, so the high content of three biogenic amines in the avian thalamus and hypothalamus appears to result from monoaminergic fibres which end and synapse in the thalamus and hypathalamus. And in the same way as the sympathetic ganglion cells innervated by cholinergic neurones responds to acetylcholine, that is, they are cholinoceptive, so should the cells in the hypothalamus innervated by monoaminergic neurones be monoaminoceptive, that is, they should respond to monamines. And actually they do.

Marked species variation in respect to the central actions of these three biogenic amines have been reported by several workers. Feldberg and his colleagues (1963 & 1967) have reported that in cats, dogs and monkeys 5-HT raises and catecholamines lower the body temperature, which, when viewed in more general light, the humoral control concept in thermoregulation may be considered as an extension of the trophotropic-ergotropic-amine behavioral control hypothesis advanced by Brodie et al. (1959). But results obtained in other

species contradict this. In rabbits and sheep catecholamines have been noted to cause rise and 5-HT to lower body temperature (Cooper et al, 1965 & Bligh, 1966), whereas in goats and oxen on the other hand, 5-HT has marked hypothermic action and catecholamines ineffective (Anderson et al, 1966 and Findlay & Robertshaw, 1967). In rats and mice both 5-HT and catecholamines appear to play heat loss hypothalamic neurotransmitter role.

According to Allen & Marley (1966-67), catecholamines raise, though inconsistently and 5-HT produces brisk fall or is ineffective on rectal temperature of chickens. (The implication of these species differences is that monoaminergic neurones activated for a given temperature regulating function in the hypothalamus apparently use different monoamines and that it is not possible to apply results obtained in one species to another.)

Because Allen & Marley (1966-67) have given these amines by systemic route, it is not possible to draw any conclusion on account of the blood brain barrier (BBB) with respect to these amines and the effect of ambient temperatures.

Therefore, in the present investigation 5-HTP

(precursor of 5-HT) and dopamine (immediate precursor of NE & EN) in heavy doses have been employed to study their effects on rectal temperature of young W.L.H. birds at different ambient temperatures. Since, vascular responses and gross behavioural changes are related to the changes in body temperature, effects of these compounds on vascular responses and gross behavioural changes have been also studied. Results of present investigations may disclose the species variation with respect to the transmitter role of these amines in thermoregulation and also may have some important bearing on poultry production and management.

CHAPTER II

REVIEW OF LITERATURE

REVIEW OF LITERATURE

A. REGULATION OF BODY TEMPERATURE IN BIRDS

Birds like mammals are homeotherms, that is, they can maintain a near constant body temperature irrespective of the environmental temperatures. The maintenance of temperature within prescribed range under varying conditions of thermal loads is accomplished by a special nervous mechanism which regulates a number of physiological functions. The complex regulation of physiological processes which balances thermogenesis and thermolysis in the body and, therefore, ensures maintenance of a constant body temperature may be termed "thermo-regulation". This does not necessarily mean maintenance of constant heat, that is, no heat storage. In fact, as a homeotherm grows from conception to maturity, there is large increase in heat content due to increase in mass. The body heat-content may be expressed as follows ;

$Q = MST$, where, Q is the heat content, M is the mass, and T is the average body temperature which equals 0.33 mean skin temperature plus 0.67 core temperature monitored by rectal temperature ($TA = .33\ Ts - .67\ Tr$). It is seen that a constant value of T does not ensure a constant value of Q.

By about seventh day after hatch, chicks have been found to develop some measures of temperature control, but the control system is not fully developed, until the down feathers are replaced by juvenile plumage at about 3 weeks of age (Moreng & Shaffner, 1951). Deep body temperature of birds is generally higher than that of mammals, with a range of 41.2°C to 42.2°C as compared to 36.4°C to 39.4°C for common domesticated mammals (Whittow, 1965). King & Farner (1965) have emphasized that only the deep body, "the core" - is held within narrow temperature limits, while "the shell" may vary from the ambient temperature to that of the core. Most thermogenesis occurs in the core while most thermolysis occurs from the shell.

Heat may be lost from the body in two general ways, directly through radiation, conduction and convection or indirectly, as the result of evaporation of moisture (physical control).

1. Direct Control

Birds, as nonsweating animals, normally lose heat from the shell by direct transfer to the environment, and evaporative losses from the shell are not extensive. Rates of heat loss by direct transfer are related to the temperature gradient between body surface, ambient

air and objects in the environment (Whittow, 1965), which is in agreement with Newton's law of cooling. (The law may be expressed as, H(Kcal/hrs) = C(Ts-Ta) where, C is a constant referring to the exposed area and surface geometry, Ts is the mean skin temperature, Ta is the ambient temperature and H is either heat sink or heat source). Thus, mechanisms which control skin temperatures and the insulating, properties of the surface layer are important. Skin temperatures in areas covered by feathers remain close to that of the core in a wide range of environmental temperatures (Irving & Krog, 1955; Steen & Enger, 1957) but temperatures of nonfeathered extremities are more variable (Wilson et al, 1952; Enderstrom & Brumleve, 1964). Heat loss in defeathered birds has been found to be two to three times more than that of intact birds and the metabolic rate in these individuals are higher (Whittow, 1965). Thus, the involuntary "erector plumorum" muscles which produce movement of individual feathers as well as the voluntary cutaneous muscles for generalised skin movement, are important in heat exchange.

Vascular convection, in which the blood acts as the transporting vehicle, due to its high-heat conductance, accounts for a great deal of the transfer of heat from the tissues to the body surface at the ambient

temperature below the upper critical limit. Arterio-venous anastomoses in the skin are sensitive to the sympathetic constricter nerve stimulation and their main function is to vary blood flow through the skin (Whittow, 1965). As reported by Guyton (1966) zero to thirty per cent of blood from total cardiac output may flow depending upon the sympathetic nerve activity. Dilation of the surface vessels allows greater flow and thus more heat is dissipated, while in cold environment, blood flow is restricted and body heat is conserved. With a feather control operating concurrently with the cutaneous blood flow, the bird utilises its physiological mechanisms most efficiently.

Vasomotor control of the surface blood supply is most important for regulating heat transfer to environment in those areas deficient in feathers (Irving & Krog, 1955). Blood vessels in the shanks of pheasants, wading birds and geese act as counter-current heat exchanger or retia thereby influencing heat loss (Enderstrom & Brumleve, 1964; Irving & Krog, 1955). Higher environmental temperature increases and lower environmental temperature decreases the peripheral thermal conductance of the body. In neutral zone in which neither increased metabolic rate or increased evaporative heat-loss is required, minor adjustment in tissue

thermal conductance maintain thermal balance. The comb may play a role in heat transfer. It has been found larger on chicken reared at lower temperature (Lamoreux, 1943). Although the removal of the comb or varnishing it failed to reduce body temperature in hot or cold environments (Lee et al, 1943), less huddling was observed during cold weather in birds with combs removed (Siegel & Beane, 1961). This suggested that while the appendages did not have influence on heat production, heat was lost from the highly vascular part and was compensated for by behavioral or other means of heat conservation.

Behaviorally, birds reduce heat loss by covering unfeathered portions of the body with feathered portions. Huddling also reduced heat loss as reported by Klieber & Winchester, (1933). In cold environments birds have been found to fluff-out the feathers (Hutchinston, 1954), thereby increasing the insulating layer of air, and conversely, tended to flatten the feathers close to the body during hot periods.

The velocity of air passing over to body is a factor in heat exchange. Rapid passage of air increases convective heat exchange and velocity sufficient to ruffle feathers disrupts the insulative still-air blanket.

At environmental temperatures upto 40°C with a velocity of 150 metres/minute, body temperatures of chickens increased less, with less dependence on respiratory evaporation than in a velocity of 15 metre/minute (Siegal & Drury, 1968a), when ambient temperatures were higher than that of body, however, high air velocity proved to be detrimental; body temperatures were sharply increased and survival times reduced (Siegel & Drury, 1968b).

2. Indirect heat loss

When environmental temperatures were found to equal or surpass body temperature, bird depended primarily on evaporative heat loss (Barrot & Pringle, 1946). Below the upper critical temperature, evaporative heat loss depended upon the respiratory surface area and vapour pressure differential between the evaporative surface and the air (Burton & Edholm, 1955). As the body of the fowl is not water proof so insensible perspiration is also a way of heat loss to the environment. The role of foecal and urinary water during heat stress has not been adequately estimated. Panting due to exertion or hyperthermic polypnea was found to be associated with heat loss even though tidal volume decreased to as low as one third of the normal (Frankel et al, 1962). The reduction in tidal volume was thought

to restrict the hyperventilation, thus avoiding the alklosis resulting from excess loss of CO_2 from blood (Whittow, 1965).

In hot environments rate of water loss (evaporative and excretory) exceeded the production of metabolic water (Bartholomew & Dawson, 1954a). Therefore, survival especially in high temperatures depends upon the availability of water. The ability of White Leghorn birds be withstand higher temperatures has been attributed to the willingness of this breed to drink large amounts of water (Lee et al, 1945; Fox, 1951) or to a better evaporative cooling mechanism (Ota & McNally, 1961). Whether or not this is related to hypothalamus has not been defined.

Evaporative heat loss has been reported to be an exponential function of ambient temperature (Barrot & Pringle, 1946) and was impeded in humid environments (Hutchinson, 1954). Thus, the ratio of heat lost by evaporation to that lost by direct means is lower in such environments.

3. Chemical Control

Increased production of heat by metabolic processes occurs when physical thermoregulation alone cannot prevent reductions in core temperatures due to

low environmental temperature. This is consequential to increased muscle tonus and increased skeletol muscle activity resulting from shivering or voluntary activity. Specific dynamic action which occurs during digestion was found to increase metabolic rate by 15 to 18 per cent in 'fowl' (Barrot et al, 1938). Steen & Enger (1957) in their studies in the pigeon, found pectoral muscle action potentials to reflect elevated heat production in cold without shivering. However, increased respiratory and cardiovascular activities may also increase metabolic heat production during hypothermia. Thermolysis must exceed thermogenesis if control is to be maintained. On the other hand, under the action of high environmental temperatures metabolism decreases which is one of the ways of fighting over-heating.

4. Neural control of temperature regulation

The striking observation that over a wide range of thermal stress, from extreme heat to extreme cold, the core temperature may vary only a fraction of degree (C) emphasizes the precision of control centres in calling forth proper effector mechanism. The mass of experimental evidence reviewed by Hardy (1961), such as pathological lesions and other experimental procedures ranging from crude-extirpation to production of precise electrolytelesions, localised electrical stimulation

and localised heating and cooling indicate that primary control centres for temperature regulation lie in the hypothalamus.

With lesions in the anterior hypothalamus animals as described showed marked tendency towards overheating in warm environment, but could maintain temperature in cooler environment. Extensive posterior hypothalamic lesions generally produced poikilothermic mammal which both overcooled and overheated. These observations lead to the concept of the following :-

(a) An anterior hypothalamic "antirise centre" controlling panting, sweating and vasodilation with its efferent outflow passing through the lateral posterior hypothalamus, and

(b) A posterior hypothalamic "antidrop" centre which control shivering and vasodilation. However, it has been emphasized that this separation is not clear cut, and seems to be unreasonable on account of considerable interaction and reciprocal inhibition that take place. For example, with appropriate stimuli calling forth cold protection mechanisms in dog and cat, the excitability of areas responsible for panting has been found to be abolished.

Hardy et al. (1964) have reported the electrophysiological evidence demonstrating the presence of

temperature sensitive neurons in the preoptic areas of dogs some of which (80 per cent) showed a sensitivity to temperature by increased firing rate on heating and decreased on cooling (hyperthermia detectors), while others (20 per cent) increased their firing rate with cooling(hypothermia detectors).

The additional evidence for the existence of warmth and cold sensitive elements in the hypothalamus has been also obtained by behavioral thermoregulation studies in cats and pigs (Carlisle, 1966 & Baldwin et al, 1967).

The evidences that heat production and heat loss centre is located in the thalamus and hypothalamus of birds as in mammals have been reported by many workers. Application of cold directly to the thalamic area of pigeons caused shivering (Rogers, 1923), and destruction of the diencephalon removed this response. Hyperthermal panting response was abolished in birds by abalation of thalamic areas (Rogers & Lackey, 1923). Cooling the blood before it reached hypothalamus prevented panting even when the remainder of the body was warmed (Randall, 1943). Rogers (1928) stimulated directly the hypothalamus of the decerebrate pigeons with various stimuli (application of cold and electric stimulation) and found mostly shivering and in some cases mild panting with

electrical stimulation.

Because electrical stimulation of some of the hypothalamic regions evoked antirise and cooling and electrical stimulation of another areas evoked anti-drop response, functional thermal detectors of some sorts must be present in or near the hypothalamus of birds as well. At present little is known about the nature of these detectors.

Vagus nerves in pigeons have been reported to implicated as afferent pathway since bilateral vagotomised birds failed to increase heat production when body temperature was brought down (King & Farner, 1961). This finding suggests the possibility of deep body thermal receptors acting as core temperature monitors. Possibility of the existence of such receptors in mammals has been also described by Bullard (1966).

Shivering in chickens before reduction in deep body temperature, on exposure to low temperature has been reported by Randall (1943) suggesting the existence of peripheral receptors. These thermal receptors in birds may be special type of nerve endings like <u>end bulbs of Krause</u> (cold receptors) and <u>end organs of Ruffini</u> (warm receptors) or naked type of nerve endings as in mammals, described by Guyton (1966). Thus, it seems to be apparent that signals which activate hypothalamic

temperature regulating centre come from two or possibly three sources in birds.

Relative importance of peripheral thermal receptors has been an area of active research and Guyton (1966) has mentioned that when thermal receptors of the skin are strongly stimulated either by cold or heat, the afferent impulses travel via the dorsal roots and the spinothalamic tracts either to the thalamus and then to hypothalamus or directly to hypothalamus and interact with hypothalamic temperature regulating mechanisms to reset the control level of hypothalamic thermostat slightly below in hot and slightly above (only fractions of a degree C.) in cold and thus make the thermostat more effective. Besides, these sensations cause a psychic desire for warmer surroundings and also elicit local cord reflexes that affect blood flow to the skin and thereby help to maintain temperature. However, it would be impossible for peripheral receptors alone to regulate internal body temperature. This fact follows from basic understanding of the control principles. "Stable operation of control system requires that receptors exciting control system detect factor that is being controlled." In this instance the factor that is being controlled is the internal body temperature. Therefore, even though skin receptors

are valuable adjunct in controlling internal temperature, they do not detect this temperature and thus, cannot substitute for hypothalamic thermostatic control system.

Hardy (1961) has differentiated the different zones of regulation into vasomotor control (neutral zone), evaporative and vasomotor control (hot zone) and control of metabolic rate (cold zone). The regulation of body temperature in cold and neutral zones as suggested are largely affected by action of peripheral receptors whereas regulation in hot zone and during activity is governed by central receptors.

5. Hypothalamic integration with effector neural mechanisms

Thermo-regulation is based on the principle of negative feed back automatic biological control systems i.e. "Servo Control". Here, magnitude of regulated variable (existing temperature of the system) is sensed by the thermodetectors in the hypothalamic thermostat and compared with reference level which is desired or is optimal called "set point temperature" (the temperature at which the activities of various antirise and antidrop detectors are equal and opposite) in such a manner that an error signal develops in case discrepancies exist, which is then fed back to the effector mechanisms such

as autonomic, somatic, endocrine and behavioral, in negative or inhibiting manner. And finally, the effectors respond at the controller command to a difference between the "set point temperature" and temperature of the system i.e. load error to minimise the same.

(a) Hypothalamic integration with effector mechanisms producing antirise responses

When preoptic thermostatic temperature i.e. the magnitude of the regulated variable exceeds the set point temperature due to flow of warm blood, an error signal develops which is fed in an inhibiting manner to the effector mechanisms resulting into the following :-

(i) Increased sweating due to volley of efferent sympathetic impulses to sweat glands,

(ii) Increased panting and salivation due to efferent outflows acting via the respiratory centres closely associated with parasympathetic stimulation of salivary glands, and

(iii) Vasodilation of the skin by activating sympathetic vasodilator outflow and by inhibiting sympathetic centres in the posterior hypothalamus which removes normal vasoconstrictor tone to the skin vessels & therefore, allows still more vasodilation.

(b) Hypothalamic integration with effector mechanisms producing antidrop responses

When preoptic thermostat of hypothalamus is cooled below the "set point temperature" by the flow of blood, an error signal is generated which set special mechanisms into play to conserve the heat that is already in the body and to increase the rate of heat production through shivering and nonshivering thermogenesis as follows :-

(i) Heat conservation by -

Vasoconstriction - due to the release of posterior hypothalamic areas from inhibition by preoptic thermostatic signals, as a result sympathetic areas become overactive and intense generalised vasoconstriction due to heat ensues, causing decrease in peripheral conduction.

Piloerection - resulting from the stimulation of sympathetic centre and efferent out-flows reaching the "erector plumorum" muscles causing contraction, and,

Complete cessation of sweating in sweaters and decreased salivation and panting, thus stopping the evaporative cooling except that resulting from insensible perspiration.

(ii) Increased calorigenesis due to -

Increased activity of sympathetic activity with release of norepinephrine and epinephrine causing calorigenic action,

Increased. T.S.H. production and release which in turn stimulates more thyroxine output from thyroid leading to enhanced cellular metabolism, and

Stimulation of primary shivering centre in the dorsomedial wall of third ventricle which normally remains inhibited by signals from preoptic thermostat. However, when preoptic thermostat becomes cooled and thereby loses its excitation, the normal inhibition of the primary motor centre no longer exists. The self excitation property of this centre thus causes it to transmit signal to the anterior motoneurous causing fascilation which in turn increases muscle tone and causes muscles to contract. Shivering probably results from the feed back oscillation of muscle spindle stretch reflex mechanism.

B. BIOGENIC AMINES

1. The occurrence of the three biogenic amines in the hypothalamus

If changes in the body temperature are mediated through the release of three biogenic amines, that is, 5-hydroxytryptamine (5-HT), norepinephrine (NE) and epinephrine (EN), their presence in the hypothalamus is a must. And they are.

The presence of biogenic amines and some of their acid metabolites such as vanillomandelic acid (VMA) formed from catecholamines and 5-hydroxyindol acetic acid (5-HIAA) derived from 5-HT in the mammalian as well as in avian hypothalamus has been investigated by several workers and their presence has been established. The values obtained with respect to the concentration in the hypothalamus of different species of animals and human-being by different investigators are given in Table 1.

The occurrence of biogenic amines has been also reported in the diencephalon of hedgehog - a poikilotherm but their concentration varied at different times of the year (Uuspaa, 1963 a,b). In winter during hibernation, the level of NE in the diencephalon was lower and that of 5-HT higher than in summer during the waking state.

TABLE 1

Distribution of biogenic amines, their acid metabolites and enzymes concerned with their synthesis and inactivation in the hypothalamus

Species	NE	EN	DPM	5-HT	HVA	5-HIAA	Dopa & 5-HTP decarboxy-lase	MAO	COMT	Refer-ence
Dog	(1) 1.03	-	(2) 0.26	(3) 1.7	-	-	(4) 117	(5) 1624	-	1-5
Cat	-	-	-	(6) 2.5	-	-	(7) 750	-	-	6-7
Monkey (Mid-brain)	(8) 1.25	-	-	(8) 0.77	-	-	-	-	(9) 0.73	8-9
Man	(10) 1.1	-	-	(11) 0.32-1.53	-	-	-	-	-	10-11
Pigeon	1.5	0.4	0.4	0.77	0.1	0.32	-	-	-	12
Pigeon (mid-brain plus optic lobes)	-	(13) 5.08	(13) 1.5	(13) 4.76	-	-	(14a) 0.26	(14b) 20.8	-	13-14a, 14b.
Chicken	1.4	1.0	0.1	0.77	0.1	0.32	-	-	-	12
Chicken	-	-	-	0.82	-	-	-	-	-	15

TABLE 1 (Cont'd)

1. mcg/g (Vogt, 1954).
2. mcg/g (Carlsson, 1959).
3. mcg/g (Bogdanski, et al, 1957).
4. mcg/5-HT formed/g/hr (Bogdanski et al, 1957).
5. mcg/5-HT destroyed/g/hr.(Bagdanski et al, 1957).
6. mcg/g (Kuntzman et al, 1961).
7. mcg of dopamine formed/g/3 hr (Kuntzman et al, 1961).
8. mcg/g (Pscheidt et al, 1964).
9. micromoles metanephrine formed/kg/90 mts (Axelrod et al, 1959).
10. mcg/g (Sano et al, 1959 & Bertler, 1961).
11. mcg/mg (Bogdanski et al, 1957; Costa & Aprison, 1958).
12. mcg/g (Jurio & Vogt, 1967).
13. micromoles/g/hr (Aprison et al, 1965).

14a. micromoles of 5-HT/g/hr (Aprison et al, 1964).

14b. micromoles of tyramine went under deamination/g/hr (Aprison et al, 1964).

15. mcg/g (Pscheidt & Haber, 1965).

Monoamines have been also detected in the extracts prepared from the anterior hypothalamus alone (Vogt, 1954; Amin et al, 1954; Kuntzman et al, 1961 and Bertler, 1961).

2. Storage and release of biogenic amines

Using the fluorescent histochemical and brain-lesion techniques existence of monoaminergic (Catecholaminergic and tryptaminergic) neurones in the mammalian as well as in the avian brain has been reported by several workers (Carlsson et al, 1962; Dahlstrom & Fuxe, 1964; Anden et al, 1965 and Jurio & Vogt, 1967). These workers have shown that biogenic amines can be made fluorescent by treating with paraformaldehyde and doing this catecholaminergic neurones exhibit green fluorescence in contrast to the yellow fluorescence elicited by tryptaminergic neurones. With the help of such studies, it was further revealed that these amines in the hypothalamus are located mainly not in the nerve cells but in the nerve fibers and endings as neurotransmitter substances.

As described by Koelle (1965) NE in the nerve terminals is stored in the osmophilic chromaffin granules (fuscogenic cells) and these granules 0.05 to 0.2 microns in diameter have been isolated from splenic

nerve and adrenal medulla containing high concentration of catecholamines (approximately 7 per cent of wet weight) and adenosinetriphosphate (ATP) in the molecular ratio of 4:1. There are strong reasons to believe that acidic phosphate groups of ATP combine and neutralise the basic groups of catecholamines and this has been suggested the fundamental storage mechanism. In the brain catecholamines have been reported to occur in the chromaffin granules which are very much smaller and resemble more the vesicles which contain acetylcholine (Chruciel,1960). From kinetic studies of the uptake, retention and ultimate release of labelled NE by Dengler et al, (1961) and studies of the influence of various drugs on these processes by several workers (Kamijo, 1956; Kirshner, 1962; Potter & Axelrod, 1963 as well as Carlsson et al, 1963), it seems clear that NE within nerve terminals remain partioned into a cytoplasmic mobile pool I (approximately 40 per cent) and intragranular pools (approximately 60 per cent), through equilibria between active transport, passive diffusion, enzymatic synthesis and destruction by mitochongial amine oxidase. Intragranular reserve pool consists of catecholamine-ATP salt in equilibrium with intragranular mobile pool II. NE is released rapidly to exterior by the nerve action potential (NAP) through the mobilisation of Ca ion, with possible involvement of acetylcholine (Burn & Rand,1959).

On the basis of pharmacological data NE released by NAP seems to come from mobile pool II but this is not yet proved. Following release of NE and its action at adrenoceptive sites of effector cells, excess is removed from extracellular region largely by return of axonal terminal through active transport or through inactivation by extraneuronal catechol-O-methyl transferase (COMT).

Murray (1965) has described the storage and release of 5-HT which appears similar to NE in that there is a granular pool where 5-HT is incombination with ATP and other mobile pools from which active 5-HT is released. The various 5-HT compartments are in equilibrium, and an active storage process maintains the granular pool against a concentration gradient. Excess 5-HT is metabolised and 5-HIAA diffuses out of the cell.

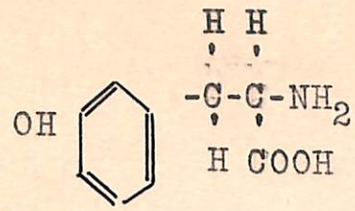
3. Occurrence of the enzymes in hypothalamus involved in the formation and inactivation of amines

When an active substance is formed in a tissue the amount present will depend upon a balance between formation and destruction or release. Therefore, enzymes concerned with its formation and inactivation should be present as well and their presence is perhaps a stronger evidence for its physiological activity than the presence

of active substance itself. Moreover, the concentration of enzymes gives an indication of the turnover of the substance.

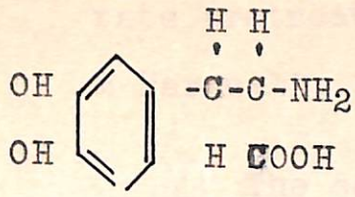
(a) Biosynthesis of amines

Catecholamines in the body are synthesised from L-phenylalanine and 5-HT from dietrytryptophan. Different steps in the synthesis of catechol and 5-hydroxytryptamine are shown in the figures on page 27a. The first step is a hydroxylation of aminoacids, tyrosine and tryptophan to dopa and 5-hydroxytryptophan (5-HTP). The enzyme for the transformation of tyrosine to dopa, "tyrosine hydroxylase" occurs in the brain and brain stem is particularly rich in this enzymes (Nagatsu et al, 1964). The enzyme for the hydroxylation of tryptophan to 5-HTP, "5-HTP decarboxylase" has been isolated from intestinal mucosal cells of the rat and guinea pig (Cooper & Melcer, 1961) and an indication for its presence has been indicated in rat liver (Freedland et al, 1961). Observations by Bertaccini (1960) on 5-HT content in the brain of totally gasterectomised rats suggested its independent synthesis in this organ. Further evidence that 5-HT synthesis occurs in the brain was more recently shown in vitro experiments with brain tissue from dogs and rabbits (Grahme-Smith, 1964) and in vivo experiments in pigeons and rats following direct administration of



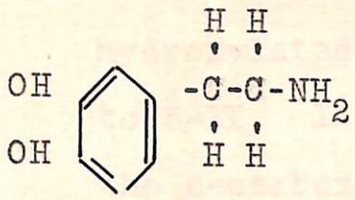
TYROSINE

(1) (Hydroxylase)

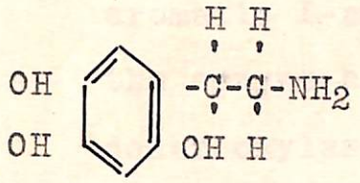


DOPA

(2)(L-Aminoacid Decarboxylase)

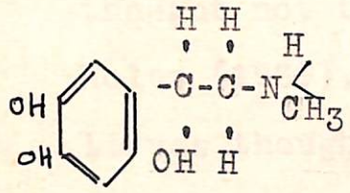


(3) B-oxidase or hydroxylase.



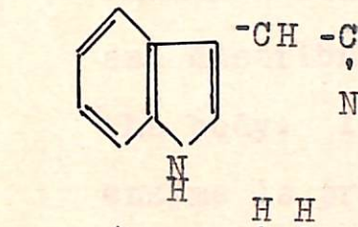
NOREPINEPHRINE

(4)(Phenylelhanol-N-methyltransferase)



EPINEPHRINE

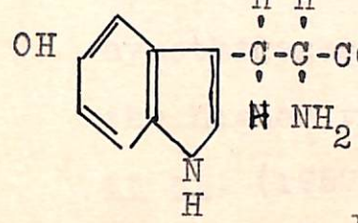
Steps in enzymatic synthesis of Norepinephrine and epinephrine.



TRYPTOPHAN

(1)(hydroxylase)

DPN
+H_2O
DPNH
+H^+

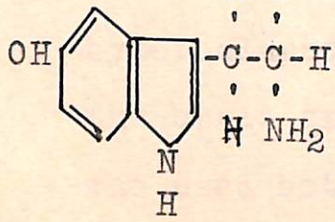


5-HYDROXYTRYPTOPHAN

(2) L-aminoacid decarbonylase

P_y ph

P_y ph & H_2O



5-HYDROXYTRYPTAMINE

1. Py ph - Pyridoxal Phosphate.

Steps in the enzymatic Synthesis of 5-HT.

radioactive tryptophan in the brain of pigeons and rats pretreated with monoamineoxidase inhibitor (Poczik & Marshall, 1963 and Consolo et al, 1965).

The second step is the decarboxylation of the hydroxylated aminoacids, dopa to dopamine and 5-HTP to 5-HT. It is now known that the same enzyme catalyses the decarboxylation reaction of all naturally occurring aromatic L-amino-acids (Lovenberg et al, 1962) and hence, the enzyme has been termed 'aromatic-L-amino-acid decarboxylase'. Originally and for a long time it was thought not to be so. When enzyme was discovered by Holtz (1939), it was named 'dopa decarboxylase' because it was thought to act specifically on dopa. It was not until 1956 that the first systematic study was made by Gaddum & Giarman (1956) of the formation of 5-HT from 5-HTP and distribution of '5-HTP decarboxylase' throughout the body. In this investigation it was shown that the enzyme is present in the high concentration in the hypothalamus of dog and ox. The same result but even the higher values were obtained for dog by Bogdanski et al, (1957, 1958) and for the cat by Kuntzman et al. (1961). In the experiments of Bogdanski et al, the hypothalamus gave higher values than any other part of the brain except caudate nucleus, and Kuntzman et al. who used both dopa and 5-HTP as substrates for measuring enzyme activity, found the enzyme also in the anterior

hypothalamus and about the same concentration as in the posterior part. '5-HTP decarboxylase' activity was also determined in liver and discrete areas of the brain of pigeon by Aprison et al. (1964). These workers found that except for very low enzyme activity in the cerebellum, other three brain areas (telencephalon, diencephalon plus optic lobes and medulla oblongata plus pons) possessed enzyme activities which were relatively constant, highest being in the diencephalon and telencephalon. However, the enzyme activities in these three brain parts (0.19-0.26 micromoles/g/hr) were less than half the activity obtained for liver (0.57 micromoles/g/hr).

Hydroxylation of dopamine at Beta-Carbon inside chain leads to NE and the enzyme catalysing this reaction 'dopamine Beta-oxidase' or 'dopaminehydroxylase' has been identified in the extracts prepared from dog hypothalamus (Udenfriend & Crevling, 1959).

Methylation of NE finally leads to the formation of EN, the reaction being catalysed by 'Phenyl ethanolamine N-methyltransferase' and S-adenosylmethionine acting as methyl donor. This enzymes occurs in the adrenal medulla and its non-occurrence in the sympathetic nerves of most animals is in accord with fact that in most animals only NE is the transmitter of sympathetic

adrenergic nerves. Axelrod (1962) detected minute amounts in the extracts of mid-brain of rabbits. This finding with low content of EN in the brain stem (Vogt, 1954) is suggestive of the fact that the main adrenergic transmitter in the central neurones is NE and not the EN. On the other hand McGeer & McGeer (1964) found enzyme activity in homogenates from brain-stem and hypothalamus of rabbits higher than Axelrod (1962) when they used his method but with a radioactive coenzyme S-adenosyl methionine-methyl-^{14}C of higher specific gravity in their homogenates. Some indication of N-methyltransferase activity in brainstem of cats and monkeys was obtained in vivo experiments after an injection of ^{14}C tyrosine or ^{14}C NE into the brainstem. Radio active epinephrine was detected in homogenates prepared from this part of the brain when animal was killed a few hours later (McGeer et al, 1964).

(b) Inactivation of amines

The enzymes involved in the degradation of catecholamines are 'monoaminooxidase' (MAO) and 'Catechol-O-methyltransferase' (COMT). MAO and 'aldehyde dehydrogenase' are common enzymes involved in the inactivation of catechol and indolamines.

'MAO', a mitochondrial enzyme, found particularly

at the sites of formation and storage of biogenic amines, metabolises catecholamines and 5-HT into their corresponding aldehydes (Catechol and indol) with loss of ammonia through a process called 'oxidative deamination', 'Aldehyde dehydrogenase' then catalyses the oxidation of aldehydes into corresponding acid metabolites such as vanillomandelic acid and S-hydroxyindol acetic acid as shown in the figures on page 31a.

'COMT', a soluble microsomal enzyme transfer one methyl group from S-adenosyl methionine as the methyl donor to one of the hydroxyl groups of catechol rings as illustrated in the figure on page 31a.The compounds formed by the action of 'COMT' on EN and NE are metanephrine and normetanephrine.

Previously 'MAO' was thought to be the main enzyme for inactivation of catecholamines. However, circulating EN and NE are certainly inactivated by COMT. Further finding that 'MAO' inhibition does not potentiate or prolong the effects obtained on stimulation of adrenergic sympathetic nerves, suggested involvement of 'COMT' in inactivation of NE released from peripheral adrenergic fibers.

Pletscher (1966) have suggested that both the enzymes are involved in inactivation and that MAO seems to inactivate the catecholamines released from pool with slow turnover which presumably represents the major

Fig. showing steps in inactivation of catecholamines.

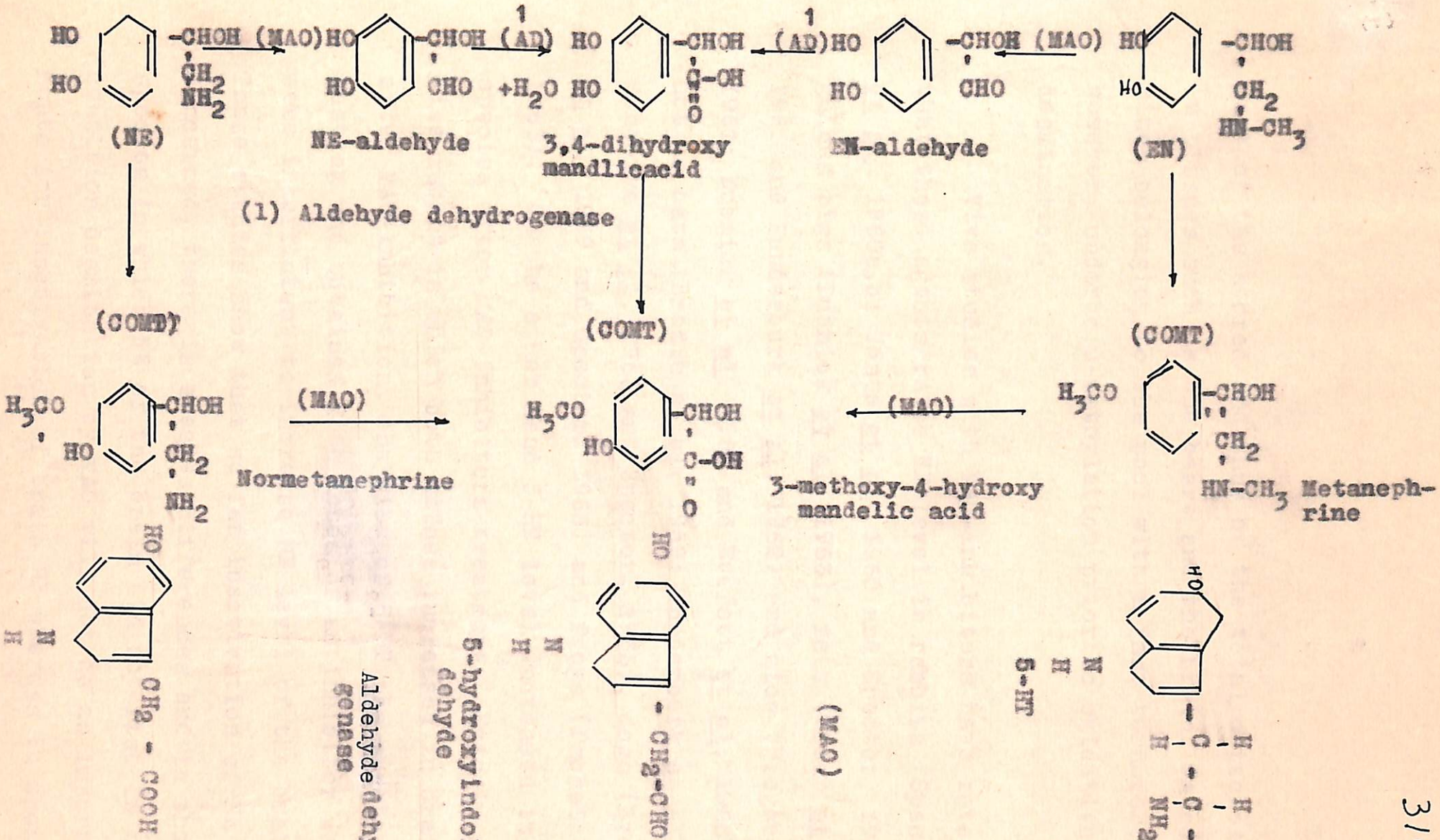


Figure showing steps in enzymatic degradation of 5-HT in brain.

part of the stored and thus of the total catecholamines in tissues such as the heart and the brain. Catecholamines belonging to the pool with a fast turnover, however, undergo O-methylation prior to oxidative deamination.

Vivo studies with MAO-inhibitors have revealed that these agents raise NE level in rabbits (Spector et al, 1960a,b; Costa et al, 1960 and Spector, 1963), guinea pigs (Dubnick et al, 1963), rats (Crout et al, 1961 and Funderburk et al, 1962) and mice (Wiegand et al, 1961; Dubnick et al, 1963 and Everett et al, 1963), but not in cats (Brodie et al, 1959; Funderburk et al, 1962; Schoepke et al, 1963 and Spector, 1963), dogs (Brodie et al, 1959 and Spector, 1963) and frogs (Pscheidt, 1963). On the other hand 5-HT level increased in all species after MAO-inhibitors treatment. Even in species like rabbit in which both amines increased in brain after MAO-inhibition, the rise of 5-HT was greater longer lasting and obtained with doses of an inhibitor which were insufficient to increase NE level of the brain. These studies show that so far inactivation of NE is concerned, there is species differences and in those species in which NE of the brain did not rise in this condition deamination by MAO will not be an important route for inactivation of brain NE whereas in those rise

occurred, MAO must be active without necessarily excluding the alternate route of inactivation by COMT.

'MAO' was first identified in 1928 by Hare in liver extracts (using tyramine as substrate). Its action on EN was described by Blaschko et al. (1937a,b) and on 5-HT by Blaschko (1952). The rate of oxidation of 5-HT was about the same as that for tyramine and greater that for EN. The distribution of 'MAO' in brain has been studied by several workers. Aprison et al.(1964) studied the MAO-activities in discrete areas of pigeon brain and reported that the activities for the telencephalon, mid brain, pons and medulla oblongata varied a little between 16.5-20.8 micromoles/g/hr and that for cerebellum 8.2 micromoles/g/hr, was less than the half of the other parts. However, the MAO-activity of liver (44.5 micromoles/g/hr) against tyramine was approximately 2-3 times the activity of the brain. In dog brain, Bogdanski et al, (1957) using the 5-HT as substrate found highest activity in the hypothalamus. Weiner (1960) too, found the enzyme most highly concentrated in the hypothalamus of dog, ox and man. The same result, but with histological method was obtained in mouse by Arioka & Tainamukai (1957).

'COMT' was first found in rat liver by Axelrod (1957). It also occurs in the brain of rat but in much

lower concentrations (Crout et al, 1961). Detailed studies concerning its occurrence in different parts of the brain and in the brain of different species have not been performed. Evidence for COMT activity in the brain of cat has been obtained by Mannario et al. (1962). A few hours after an injection of NE ^{14}C in the lateral ventricle of cat, they could isolate in the brain tissue not only radioactive NE but also radioactive normetanephrine.

The effect of pyrogallol an inhibitor of COMT has been examined on the NE content of brain rats and rabbits. Neither intraperitoneal injection of Pyrogallol increased the brainstem NE in rats (Crout et al, 1961) nor did intravenous injection in rabbits. But when they were combined with injections of dopa, which by itself was ineffective, they caused a two to three fold increase in brain NE (Weil-Malherbe et al, 1961), given intracisternally to rabbits, Pyrogallol alone greatly increased the brain stem NE (Matsuoka et al, 1962).

4. Temperature responses to three biogenic amines administered by intracerebroventricular (ICV) injections or by intra-hypothalamic (IHT) microinjections

The first pioneer study in this direction was done by Feldberg & Myers (1963, 1964a) on concious cats.

These workers administered drugs through intracerebro-ventricular canula. A dose of 200 microgramme of 5-HT produced biphasic rise in rectal temperature associated with shivering. Initially there was immediate but transient rise which returned to normal and after an hour there was a second more gradual but prolonged elevation upto 2'C lasting for nearly 18 hours. Cessation of shivering was also noticed during the intermediate hypothermic phase. 5-HT coadministered with pyrogen showed synergistic effects. On the other hand when NE and EN injected in the doses of 50-10 microgramme lowered temperature particularly when it was raised previously by pyrogen or 5-HT. The hypothermic effect of these agents was observed within few minutes and the peak fall within 45 minutes.

The ability of catecholamines to abolish and 5-HT to produce shivering when injected ICV was observed before their temperature effects were discovered (Domer & Feldberg, 1960), and at that time dopamine was found much less potent than either NE or EN in abolishing shivering.

Kulkarni (1967) injected ICV solution of 5-HT in distilled water instead of NSS and found hypothermic effect in cat. This hypothermia was more aggravated

when larger doses of 5-HT in distilled water were used. Benerjee et al. (1968) reported that even with large doses of 5-HT injected in distilled water fall was followed by a rise in temperature beyond preinjection level in cat.

Feldberg & Myers (1965a) applied 5-HT unilaterally to the region of anterior hypothalamus by microinjections in the doses of 2 microgramme in cat and observed long lasting hyperthermia associated with shivering, constriction of ear vessels and acceleration of respiration. The temperature began to rise within one minute of injection and was often biphasic. Microinjections 2.5 and 5 microgramme of EN and NE respectively caused fall in temperature the extent of which depended upon the doses and EN was twice as potent as NE. The hypothermic effect was obtained in normal as well as in those animals in which temperature was previously raised by typhoid vaccine or 5-HT injected into anterior hypothalamus. When these drugs were similarly applied on the posterior part of hypothalamus no temperature change was noticed.

Effects of biogenic amines have been found variable as shown below :-

	Cat (1)			
	Dog (2)	Rabbit(4)	Ox (6)	Rat (8)
	Monkey(3)	Sheep (5)	Goat(7)	Mouse (9)
Catecholamines	↓	↑	—	↑↓
5-HT	↑	⇣	↓	↓

1. Feldberg & Myers (1963, 1964a).
2. Feldberg, Hellon & Myers, (1966).
3. Feldberg Hellon & Lotti, (1967); Myers,(1967b).
4. Cooper Cranston & Honour, (1965).
5. Bligh (1966)
6. Findlay & Robertshaw (1967).
7. Anderson, Jobin & Olsson (1966).
8. Feldberg & Lotti (1967b).
9. Brittain & Handley (1967).

Direction of arrows indicates hypo (↓) or hyperthermia (↑). Dotted arrow indicates weak and inconsistent action.

The hypothalamus of dog and monkey responded to three biogenic amines in the same way as that of cats when administered into the cerebral ventricles although in unanaesthetised animals hyperthermic effect of 5-HT was observed with small doses under 20 microgramme only (Feldberg et al, 1967). And in unanaesthetised monkey, Myers (1967b) found that 5-HT injected into lateral or 3rd ventricle or into the anterior hypothalamus, produced fever only when used in small dose (5 microgramme) ; with large dose (10 microgramme) there was a transient but marked fall in rectal temperature followed by a negligible rise, a result which resembled that seen in cats.

Cooper Cranston & Honour (1965) observed that 10-microgramme of NE injected into lateral ventricles or into the anterior hypothalamus of concious rabbits, either caused a rise in temperature or had no effect. 200 microgramme of 5-HT injected similarly either caused a fall in temperature or had no effect. When the injection was made in the anterior hypothalamus, 5-HT was effective only if temperature had been previously raised by injection of Pyrogen or NE.

In sheep, Bligh (1966) observed responses similar to in rabbits by injecting these amines into lateral ventricle.

Findlay & Robertshaw (1967) described the effects of NE and EN (3 mg each) and 5-HT (5 mg), injected into the lateral ventricles of ox (Bostaurus) on the respiratory rate, tidal volume, heat production, skin temperature of ear, evaporative loss from the skin and rectal temperature. These workers found that neither EN nor EN had any effect on the temperature regulating mechanisms of ox except to produce vasoconstriction, if vasodilation was already present due to high ambient temperature of previous injection of 5-HT. whereas, 5-HT caused a rise in respiratory rate, fall in tidal volume and heat production, elevation of skin (ear) temperature and skin evaporative loss associated with marked fall in rectal temperature with sedation.

Similar effects have been reported in goats by Anderson et al. (1966) in which injections of 5-HT into 3rd ventricle under normal body temperature as well during pyrogen induced fever were found to cause peripheral vasodilation, polypnea and marked fall in body temperature, whereas injections of small amount of catecholamines into the same site did not alter the rectal temperature significantly.

Feldberg & Lotti (1967b) injected 5-HT into the cerebral ventricles of rats in the doses of 2-20 microgramme which produced hypothermia similar to ox and goat but catecholamines were not found to be ineffective and when injected similarly produced hyper or hypothermia depending upon dosage. A rise in temperature usually preceded by a short-lasting fall was obtained with smallest effective dose (2-6 microgramme) and with increasing (10-100 microgramme) the fall in temperature became more pronounced and longer lasting and was finally the sole effect, so that catecholamines as well as 5-HT then lowered rectal temperature.

In mice effects of these amines, similar to in rats have been reported by Brittain & Handley (1967).

5. Evidence for the release of biogenic amines and their appearances in the effluent from perfused third ventricle

When substances artificially applied to an organ in which they occur naturally produce effects which mimic their physiological activity, the question arises whether it results from the release of these substances. Their occurrence in the organ and their pharmacological effects alone, however, do not prove it. It is necessary to demonstrate that they are actually released during physiological activity. It was, therefore, thought to review the evidences showing that the three biogenic amines are released in the hypothalamus and that their release is associated with changes in temperature.

Feldberg & Myers (1966) perfused the ventral half of the third ventricle of the anaesthelised cat and detected 5-HT in the effluent by using the method of Vane (1957). The contraction produced by 5-HT in the effluent, of the rat fundus strip was found to be prevented by the specific antagonist of 5-HT, 2-bromolysergic acid.

Hawary & Feldberg (1966) carried out the experiments on a pentobarbital sodium anaesthetised cat using 5-HTP-Precursor of 5-HT either injected intraperitoneally or added to the perfusing fluid to correlate the higher

concentration of 5-HT in the effluent with the temperature changes. When the temperature of the cat levelled off, the Third ventricle was first perfused with artificial C.S.F. which did not affect the temperature and the amounts of 5-HT detected in the effluent were small. But on switching over to perfusion with 5-HTP, the output of 5-HT increased greatly, the cat began to shiver and temperature climbed to fever level.

Feldberg & Lotti (1967a) used MAOI-tranylcypromine (parnate) in a chloralosed cat to investigate the effect on 5-HT output and body temperature. Injected intraperitoneally (5 mg/kg) or added to the perfusion fluid, tranylcypromine caused an increase in 5-HT output from the perfused third ventricle, associated with shivering and rise in temperature.

In several experiments in which effluent from the perfused third ventricle was assayed on rat fundus-strip preparation, the contraction produced by the effluent was preceded by relaxation. And when this result was duplicated by adding 5-HT together with epinephrine in the fundus-strip preparation by Feldberg & Myers (1966), suggested the presence of epinephrine in the effluent.

Myers (1967a) made cross-infusions of the hypothalamic perfusate from the third ventricle of a monkey

(donor) to the corresponding site of another conscious monkey (recipient) during the periods of warming and cooling. The donor monkey was cooled by placing dry ice in the chamber in which it was sitting on the chair, and its ventricular fluid was then pumped into the recipient monkey which began to shiver and its temperature rose. On the other hand when transfusion was made following heating of the donor monkey by blowing hot air in its chamber, a drop in the temperature occurred in the recipient. However, the exact nature of the substances in the transfusion fluid is still a question mark.

C. CONTROL OF BLOOD PRESSURE (BP) IN FOWL

Blood pressure of fowl is very variable particularly in unanaesthetised condition. Blood pressure of anaesthetised adult fowl with carotid canulation (Systolic, 120 and diastolic, 90 mm Hg) has been reported by Akers & Peiss (1963) and other workers which is more or less the same as that of cat, dog and man.

The control of cardiovascular activity to maintain constancy in B.P. is a classical example of a homeostatic, negative feed back system. Since, B.P. is product of cardiac output and peripheral resistance, the effector mechanism seems to be dual and, thus, it can be either lowered or increased by a reduction or increase in these two factors. The B.P. is sensed by special organs called baroreceptors located primarily in the carotid sinus and arch of the aorta (mammals). Afferent impulses from these receptors travel via afferent nerves to the cardiovascular centre. The reference system has not been clearly described. The error signals acting to correct deviation in B.P., pass via autonomic nervous system to peripheral vasculature and heart to set right the deviation. An increase in the B.P. stretches the pressoreceptors in the wall of carotid arteries, aorta and other arteries stimulating to increase the frequency of

discharge along afferent nerves to cardiovascular centre to inhibit sympathetic division action on heart and peripheral vasculature, to stimulate vagal activity resulting into reduced cardiac vigour, bradycardia, vaso and venodilation leading to fall in B.P. Conversely, in case of hypotension, B.P. goes above even the normal value by a negative feed back signal to the effectors.

1. Vasomotor centre

This centre in the mammals is situated in pons and medulla. Bilateral portions of this centre is responsible for maintaining sympathetic vasoconstrictor tone and their stimulation leads to vasoconstriction, tachycardia and hypertension. Stimulation of medial area sends inhibitory impulses to the bilateral areas thereby decreasing vasomotor tone and allowing vasodilation and brady-cardia with associated hypotension.

In birds, less is known about this centre, but there are some evidence that it is in the thalamus and stimulation of this area produces change in B.P. (Sturkie, 1954). According to Sturkie (1954) the effect of the cardioacceleratory nerve on B.P. is not yet reported but vagus is cardioinhibitory. There is report that vasomotor centre in mammals can be influenced by higher centres situated in cerebral cortex and hypothalamus.

For example, stimulation of motor areas can either excite or inhibit this centre according to the areas stimulated. Similarly, stimulation of preoptic region of hypothalamus causes decrease in B.P. and heart rate by acting through vasomotor centre. To the contrary when posterior region of hypothalamus is stimulated opposite effects are observed. Nothing seems to be known about the control of vasomotor centre from higher nervous centre in birds.

2. Reflex stimulation of B.P.

To date no clear cut carotid sinus baroreceptor reflex has been demonstrated in the chicken (McGinnis & Ringer, 1966) and probably nothing seems to be known about other baroreceptor reflexes such as 'Bainbridge reflex' (due to increase in pressure in venacava and right atrium) and 'Bezold-jarisch reflex' or 'coronary chemoreflex'(due to irrelation of left ventricle) in birds. Thus it remains an enigma as to how birds regulate B.P. in one of the most fundamental interactions with the environment. In birds, however, vasomotor centre has been stimulated by stimulating strongly the central end of sciatic and brachial nerves resulting into hypotension as in mammals.

D. TEMPERATURE AND CIRCULATORY RESPONSE OF BIOGENIC AMINES ON SYSTEMIC ADMINISTRATION

Allen & Marley (1966, 1967) observed the effects of biogenic amines on rectal temperature and oxygen consumption in conscious young (1-21 days) and adult chicken at room temperature 21°-24°C. These workers found that catecholamines (0.1 to 0.5 mcg/kg) when injected intravenously lowered temperature in young birds by 1-4°C and the effects lasted for 40-120 minutes. Oxygen consumption was also decreased but more briefly followed by transitory increase above control value. The hypothermic effect in the chicks was antagonised by phenoxybenzamine (100 mcg/kg) given intravenously. In adult birds catecholamines raised the core and surface temperature by 1-2°C or were ineffective. On the other hand tryptamine and 5-HT were either ineffective or evoked brief fall in temperature. After pretreating the young and adult birds with mebanazine (100 mcg/kg) intravenously both tryptamine (5 mcg/kg) and 5-HT (1 mcg/kg) produced rise in temperature by 2°C and 15-25 per cent increase in oxygen consumption lasting for 70-100 minutes. α methyl trytamine when given alone (10 mcg/kg) intravenously raised rectal temperature. The effects of these tryptamine compounds were antagonised by methysergide (0.01-0.1 mcg/kg) administered intravenously.

The effect of catecholamines (NE and EN) given i.p. in the doses of 200-500 mcg in rat was found hypothermic (Feldberg & Lotti, 1967b) whereas in rabbit these amines failed to alter body temperature on intravenous administration (von Euler et al, 1943).

In mice, Lessin & Parkes (1957) obtained a fall with i.p. injection of 100 mg/kg.5-HT, and Fastier et al. (1957) a fall after subcutaneous injection of 20 mg/kg. In rats marked hypothermia following i.p. injection of 8 mg/kg.5-HT was observed by Dandiya & Sellers (1961), and following subcutaneous injection by Hoffman (1958, 1959) who used 1 mg/kg. Shemano & Nickerson (1958) also found hypothermia with 3 mg/kg. 5-HT. These workers showed further that hypothermic effect could be converted to hyperthermic one by raising the environmental temperature to 30°C.

In guinea pigs, pretreated with MAO inhibitor (Hodge et al, 1964) and in pigeons 5-HT lowered body temperature when given subcutaneously (Hoffman, 1958).

Catecholamines exert a pressor response in bird as in mammals with the exception that with EN diastolic pressure is increased rather than decreased or unchanged as in mammals (Akers & Peiss, 1963). Epinephrine injected in chicks intravenously elevated systolic

blood pressure to 70 mm Hg and diastolic to 55 mm Hg Rodbard & Tolpin, 1947). Sturkie (1954) observed that increased pressure was due mainly to vasoconstriction, because it remained elevated long after heart rate came to normal.

The effect of 5-HT on the blood pressure of birds is probably not yet reported. In mammalian species including man, this agent exerts a triphasic response - a brief depressor phase immediately following the injection; a succeeding pressor phase, and finally, within 1-2 minutes of the injection a prolonged depressor phase has been described by Douglas (1965).

E. TEMPERATURE AND CIRCULATORY RESPONSES INDUCED BY AGENTS THROUGH INTERACTION WITH BIOGENIC AMINES

1. Monoamineoxidase (MAO) inhibitors

Feldberg & Lotti (1967a,b) reported that tranylcypromine (10 mg/kg) when injected i.p. produced either no effect or a small rise in cats, a rise upto 1.5°C in dogs and was ineffective in rabbits. In rats, it produced a fall in the doses of 0.1 to 0.3 mg/kg. Such injections in dogs and cats prevented the deep and long lasting fall in rectal temperature when anaesthetised with pentobarbitone sodium or chloralose later, without affecting anaesthesia. ICV injection of 1 mg produced a pronounced rise of temperature in cats and dogs but did not affect temperature in rabbits, whereas, in rats 0.03 to 0.1 mg produced a fall.

Karja et al. (1961) reported that pheniprazine had little effect on temperature in mice when injected intraperitoneally. On the other hand, DesPrez et al. (1966) found that pheniprazine often caused a spontaneous fever in rabbits. Shellenberger (1966) obtained a hyperthermic response in rabbits with the inhibitor pargyline and when brain stem 5-HT level was measured, it was found to be elevated. Further this worker observed

that hyperthermic response was greatly potentiated after the brain stem catecholamines were depleted previously by α-methylmetatyrosine.

Nialamide has been described by Krantz & Carr (1965) to be 2-2.5 times more potent than iproniazid in potentiating the pyretogenic response in rabbits to i.p. injection of 5-HTP.

Direct action of MAO inhibitors on heart is not known. A hypotensive effect of these agents resembling that produced by sympathetic blockade has been reported in mammals by Gessa et al. (1963).

2. Cyproheptadine (Periactin)

Canal & Ornesi (1961b) reported that cyproheptadine, a potent anti-5-HT when injected into rabbit intravenously inhibited the hyperthermia significantly produced by intravenous injection of bacterial pyrogen. The result was found particularly striking in experiments in which 'MAO' was blocked. It lowered the temperature in rabbit in the doses of 0.3 to 3 mg/kg. given intravenously whereas 5-HT alone gave a rise on systemic administration (Bachtold & Pletscher, 1957).

It has been reported to antagonise the pressure effect to 5-HT in dog (Stone et al, 1961).

3. Reserpine

In mammals reserpine has been reported to deplete NE (Holzbauer & Vogt, 1956) and 5-HT (Plestcher et al,1956) from the brain and peripheral sites. Similar effects have been observed in pigeon by Jurio & Vogt (1967).

Bachtold & Pletscher (1957) observed that an injection of 0.5-0.75 mg/kg of this agent lowered temperature but raised it in rabbits pretreated with intravenous iproniazid, and 1 mg/kg reserpine then produced lethal fever. According to Shellenberger (1966), intravenous reserpine caused hyperthermia followed by hypothermia, but after treatment with α-methyl-metatyrosine, this agent produced hyperthermia without subsequent hypothermia.

Cooper et al. (1967) showed that injection of reserpine 0.35-0.7 mg into cerebral ventricles of conscious rabbits raised rectal temperature associated with depletion of NE as evidenced by disappearance of fluorescence characteristic for NE. Similar findings that 5-HT is mediator of hyperthermia of bacterial origin in rabbit is based on results obtained with reserpine. Desprez et al. (1966) found that single intravenous injection of 1-1.5 mg/kg of this agent

counteracted the hyperthermia produced by bacterial pyrogen in conscious rabbit. Biochemical studies by Des Prez et al. showed that reserpine lowered the brain stem 5-HT to less than 15 per cent and NE content to about 30 per cent of the control values. Further they found that α-methyl-metatyrosine 200 mg/kg lowered the brain stem NE to approximately the same degree as with reserpine but without affecting 5-HT content, and this substance unlike reserpine did not affect the febrile response to pyrogen. However, Cooper et al. (1967) found that ICV injection of reserpine in rabbit did not abolish the pyretogenic response to intravenous bacterial pyrogen even though there was depletion of monoamines in the hypothalamus, as evidenced by the disappearance of the ultraviolet fluorescence characteristic for NE.

Kroneberg & Kurzuweit (1959) reported that when intravenous injection of reserpine was preceded by an injection of iproniazid, intravenous injection of bacterial pyrogen produced usual fever. Going (1959) observed that iproniazid given after reserpine did not restore the febrile response to bacterial pyrogen.

Benerjee et al. (1968) reported that ICV administration of reserpine (0.5-0.6 mg) caused rise in temperature in rabbit. On repeating the injection at

24 hours intervals the rise in temperature was not obtained with 2nd or 3rd injection but hyperthermic response was still observed with exogenous NE. In cats reserpine (0.5-0.75 mg) given similarly produced biphasic response, i.e. initial fall followed by hyperthermia. On repeating the injections at 24 hours intervals hypothermic phase disappeared with 2nd or 3rd injection but reappeared again when exogenous NE was given.

4. Adrenergic blocking agents

Leduc (1961) injected Phenoxybenzamine (10 mg/kg) i.p. at 3°C ambient temperature and found that animals died due to hypothermia. Similarly in rabbit a dose of 3-10 mg/kg. of this agent injected i.v. produced hypothermia (Elder & Shellenberger, 1962). On the other hand Anderson et al. (1964) failed to produce any effect on rectal temperature in goat with 10 mg/kg of this agent injected intravenously.

Leblanc & Rosenberg (1958) obtained fall in temperature in rat at 23°C with 2 mg/kg. of dibenamine injected i.p.

The actions of ergot alkloids on thermoregulation appears to be more complicated in that their responsiveness depends upon environmental temperature and types of alkloids. Ergotoxine in rat 4.5 mg/kg. injected i.p. lowered temperature at low ambient temperature and raised

it at high ambient temperature (Buchanan et al, 1950). Hydergine in rat (0.9 mg/kg.) injected subcutaneously lowered at 25°C, ineffective at 30°C and raised rectal temperature at 35°C (Shemano & Nickerson, 1958). Benerjee et al. (1968) injected ergotamine (100 mcg) into the cerebral ventricles of cats which oftenly produced a rise, but when this effect passed off, EN and NE similarly injected lowered rectal temperature.

On blood pressure of fowl α-adrenergic blocking agent such as dibenamine in higher dose (140 mg/kg.) provided only minimal adrenergic blockade without epinephrine reversal. Phenoxybenzamine was effective at 20-60 mg/kg dose level, even this represents a very large dose in comparison to most mammals except the rabbit (Harvey et al, 1954). Priscoline has been described to diminish the pressor response to EN without reversal (Sturkie, 1954).

5. Dopa and Dopamine

Kroneberg & Kurzuweit (1959) reported long-lasting hyperthermia with dopa (10-20 mg/kg) injected intravenously in rabbit pretreated with iproniazid though this agent failed to elicit temperature change alone. Similar effects were reported by Mantegazza (1964) in rat in which dopa (50 mg/kg) injected i.v.

elicited a rise after prior iproniazid and high spinal-cord transection. Giarman et al. (1968) observed that when dopa (50 mg/kg) was administered in two doses at zero hour and one hour with leucocytic pyrogen (one hour after dopa) produced an additeve pyretogenic response similar to 5-HTP except that dopa was not as hyperthermic as 5-HTP. This dose of dopa caused an increase of 75 per cent hypothalamic NE at one hour.

Uuspaa (1963a,b) injected dopa and dopamine (DPM) subcutaneously in hedgehog - a hibernating animal and found awakening effect with rise in temperature.

Dopamine is found in high concentrations in mammalian and avian tissues (Hangen, 1959 and Jurio & Vogt, 1967) and has been reported to have many pharmacological actions similar to but much weaker than EN and NE. Dopamine similar to EN exerted a biphasic effect on B.P. in dog and cat in the doses of 20-50 times higher than those of EN (Goldberg et al, 1959 and Burn & Rand, 1958) and pressor effect of both was blocked by α-adrenergic blocking agents converting it to depressor response (Mc Donald et al, 1963 and Dhasmana et al, 1969). But, unlike EN depressor response of DPM was not blocked by Beta-adrenergic

blocking agents (McDonald et al, 1963 & Eble et al, 1964). MAO inhibitors have been observed to augument the actions of dopamine, tyramine and 5-HT on heart contractile force and arterial pressure (Goldberg et al, 1959).

6. 5-hydroxytryptophan (5-HTP)

According to Udenfriend et al, (1957a,b), Bogdanski et al, (1958) and Segawa (1970), 5-HTP passes the blood-brain barrier in contrast to 5-HT and increases the level of 5-HT in the brain.

The effect of this agent on temperature has been examined in monkey, cat, rabbit, guinea pig and mouse. In anaesthetised monkey (Feldberg et al, 1967) observed a rise in temperature following an injection of this agent into the third ventricle. And in anaesthetised cat, Hawary & Feldberg (1967) found that perfusion of 5-HTP through the cerebral ventricles lead to greatly increased output of 5-HT, associated with a rise in temperature. In conscious cat also injection of 1-2 mg of this agent into lateral ventricle produced a biphasic rise similar to that seen with 5-HT.

In rabbit 5-HTP given intravenously raised temperature and the effect was greatly potentiated in animals pretreated with MAO inhibitors (Horita & Gogerty,

1958 and DesPrez et al, 1966). Without MAO inhibition a high fever was obtained with 50-100 mg/kg. by Horita & Gogerty. Giarman et al. (1968) observed the additive effect of 5-HTP coadministered with leucocyte pyrogen in rabbit associated with an increase in 5-HT level to 80 per cent of the normal value after an hour of 5-HTP administration.

Hodge et al. (1964) found that tryptophan 1 mg/kg. in guinea pig did not affect the temperature but it produced a mean rise of 3.1°C if given 18 hours after an i.p. injection of pheniprazine (20 mg/kg). Under this condition, 5-HTP produced a similar rise. The rise produced by tryptophan did not occur when its conversion to the amine was prevented by R04-4062, an inhibitor of the 'aromatic L-amino-acid decarboxylase'. The injection of this inhibitor alone caused a small fall in temperature.

Uuspaa (1963a,b) injected 5-HTP subcutaneously into hedgehog and found that this agent failed to elicit awakening and rise in temperature.

Effects of 5-HTP on circulation of dog and rabbit have been reported by Bogdanski et al. (1958). In unanaesthetised dog 5-HTP 60 mg/kg injected i.v.

produced rise in arterial pressure associated with delayed tachycardia. The rise in blood pressure particularly syslolic one remained elevated for about 2 hours. With smaller doses there was hypotension and bradycardia. In anaesthetised dog there was primary rise in blood pressure and pulse pressure, which returned to control level or was followed by prolonged hypotension. In rabbit high doses (75-100 mg/kg) of this agent caused immediate transient bradycardia and hypotension, which returned to control level within 5 minutes.

CHAPTER III

MATERIALS AND METHODS

MATERIALS AND METHODS

A. EFFECT OF 5-HTP & DOPAMINE ON RECTAL TEMPERATURE OF WLH BIRDS

To study the temperature response to 5-HTP and dopamine, White Leghorn (WLH) Young (3-4 months old) birds of either sex were used. Birds were obtained from the College farm and kept in the specially designed cage under normal husbandry conditions. Feed and water were provided ad lib throughout the experimental period. Prior to every experiment the rectal temperature was recorded twice a day for 4-5 days and the experiment was undertaken only when the resting temperature was achieved.

Rectal temperature was measured by H.B.temperature recording galvenometer and thermocouple. The thermocouple probe was inserted 2 cm into the cloaca which was held in position for 1 minute and the temperature monitored by galvenometer was recorded. During investigation rectal temperature was recorded at hourly interval for for a period of 8 hours.

Drugs were dissolved in water for injection. 5-HTP and dopamine were administered into the Wing Vein while other drugs (reserpine, nialamide, Cyproheptadine and yohimbine) were given intraperitoneally under perfect aseptic conditions. In order to standardise the effects, 5-HTP and dopamine were tested in doses of 1-2 mg and 5-10 mg respectively.

The experiments on normal birds were conducted in the following fashion -

Readings / Group	1	2	3	Number and sex ratio
I	Control	Dopamine	5-HTP	Each group consisting of 5 birds in the ratio of three female and two male.
II	Dopamine	5-HTP	Control	
III	5-HTP	Control	Dopamine	

All experiments were conducted during winter (25 ± 1°C) and summer (38 ± 1.5°C) in order to explore any variation in thermal responses of drugs to different ambient temperature.

The effect of 5-HTP and/or dopamine on the body temperature of birds at different ambient temperature were also studied on groups of 5 birds treated with -

1. Nilamide (niamid, 100 mg/kg), 12 hours
2. Reserpine (serpasil, 2 mg/kg) 1 & 48 hour
3. Cyproheptadine (periactin, 2 mg/kg)1 hour,&
4. Yohimbine (2 mg/kg) 1 hour,

prior to the administration of the test compounds.

B. EFFECT OF 5-HTP & DOPAMINE ON BLOOD PRESSURE OF WLH BIRDS

In the present investigation blood pressure was recorded according to the method described by Coon (1939) with little modification.

WLH adult birds of either sex and weighing 1.5 to 2 kg were anaesthetised with Phenobarbitone sodium (160-180 mg/kg i.m.). Crural vein was canulated and attached to burette previously filled with saline. Femoral artery was canulated and attached to the mercury manometer (Condone type) for recording the blood pressure Kymographically. Drugs were injected through canulated vein and after each injection 1.5 ml of saline was infused to push the drug into circulation.

5-HTP in doses of 20 mcg to 0.5 mg/kg and dopamine in doses of 20 mcg to 1 mg/kg were studied for their effect on blood pressure in intact as well as in nialamide (100 mg/kg) pretreated birds. Their effects on blood pressure was also investigated after atropine (0.5 mg/kg), cyproheptadine (0.7 mg/kg), Phentolamine (5 mg/kg), Yohimbine (0.5 mg/kg) and Pronethalol (0.5 mg/kg) treatment.

Effect of 5-HT (10 to 20 mcg/kg) and epinephrine (1.25 to 5 mcg/kg) on the blood pressure of fowl was also studied to compare the responses shown by their respective precursor.

CHAPTER IV

RESULTS

RESULTS

A. EFFECT OF 5-HTP AND DOPAMINE ON RECTAL TEMPERATURE OF W.L.H. BIRDS

1. Effect of 5-HTP and dopamine on rectal temperature of normal birds

(a) At 25 ± 1°C room temperature

Results of administration of 5-HTP and dopamine to normal birds are summarised in Table 1a and shown in Fig.1(A) & 2.

5-HTP in doses of 1 mg and 2 mg/kg i.v. raised the body temperature which commenced one hour after administration and lasted up to 8 hour. The maximum mean rise of 0.55 ± 0.12°C and 1 ± 0.12°C recorded at 4 hour with 1 mg and 2 mg/kg of 5-HTP respectively were statistically significant as compared to the control ($P < 0.05$ in case of 1 mg/kg and $P < 0.01$ in case of 2 mg/kg).

Dopamine 5 mg and 10 mg/kg i.v. also raised the temperature from 1 to 8 hours of its administration. The maximum mean rise of 0.55 ± 0.12°C and 0.75 ± 0.08°C with 5 mg and 10 mg/kg of dopamine respectively, recorded at 6 hour were statistically significant as compared to control ($P < 0.05$ in case of 5 mg & $P < 0.01$ in case of 10 mg/kg).

5-HTP (2 mg/kg) was found to be more hyperthermic than dopamine (10 mg/kg) and the difference between the

TABLE 1a

The effect of 5-HTP and dopamine on rectal temperature of normal WLH birds at room temperature 25 ± 1°C

Drug	Dose mg/kg i.v.	Mean rectal temperature (c) with S.E.								
		0 hr	1 hr	2 hr	3 hr	4 hr	5 hr	6 hr	7 hr	8 hr
Saline	-	41.50*	41.50 ±0.00	41.55 ±0.05	41.60 ±0.06	41.65 ±0.10	41.65 ±0.10	41.65 ±0.10	41.60 ±0.06	41.60 ±0.06
5-HTP	1	41.50	41.55 ±0.05	41.55 ±0.05	41.70 ±0.12	a42.20 ±0.12	42.00 ±0.00	41.80 ±0.12	41.70 ±0.09	41.60 ±0.06
Dopamine	5	41.50	41.55 ±0.05	41.60 ±0.06	41.65 ±0.10	41.95 ±0.19	42.05 ±0.10	b42.20 ±0.12	42.00 ±0.00	41.90 ±0.61
Saline	-	41.50**	41.66 ±0.06	41.66 ±0.06	41.75 ±0.06	41.75 ±0.06	41.75 ±0.06	41.60 ±0.05	41.60 ±0.05	41.50 ±0.00
5-HTP	2	41.50	41.90 ±0.11	42.00 ±0.11	42.30 ±0.07	c42.78 ±0.12	42.64 ±0.12	42.37 ±0.07	42.23 ±0.092	41.86 ±0.08
Dopamine	10	41.50	41.73 ±0.07	41.96 ±0.06	42.18 ±0.04	42.20 ±0.04	42.20 ±0.04	d42.40 ±0.08	42.10 ±0.08	41.80 ±0.08

* Figure indicates mean value of 5 birds.
** Figure indicates mean value of 15 birds.

a = $P < 0.05$ c = $P < 0.01$
b = $P < 0.05$ d = $P < 0.01$

maximum mean rise produced by two drugs was statistically significant ($P < 0.05$).

Control group treated with saline did not show any change in body temperature during observation period.

(b) At 38 ± 1.5°C room temperature

Results are shown in the Table 2 and Fig.1(B). The effect of 5-HTP (2 mg/kg) and dopamine (10 mg/kg) was qualitatively similar to that recorded at 25 ± 1°C but was of lesser magnitude. However, the maximum mean rise of 0.62 ± 0.05°C and 0.5 ± 0.05°C produced by 5-HTP and dopamine respectively were statistically significant as compared to the control ($P < 0.05$). Besides with both the drugs rise was delayed by one hour and decline was more gradual than at 25 ± 1°C.

2. Effect of 5-HTP and dopamine on rectal temperature of birds treated with nialamide 12 hour prior

(a) At 25 ± 1°C room temperature

The results are summarised in Table 3 and Figs.3 and 4(A).

Nialamide 100 mg/kg i.p. produced a significant mean rise of 0.56°C at 12 hour of its administration as compared to the 0 hour average normal temperature($P < 0.05$).

5-HTP in doses of 1 mg and 2 mg/kg given to

TABLE 2

The effect of 5-HTP and dopamine on rectal temperature of normal WLH birds at room temperature 38 ± 1.5°C

Drug	Dose mg/kg i.v.	Mean rectal temperature (c) with S.E. ±								
		0 hr	1 hr	2 hr	3 hr	4 hr	5 hr	6 hr	7 hr	8 hr
Saline	-	41.56	41.58 ±0.01	41.60 ±0.03	41.60 ±0.03	41.65 ±0.03	41.72 ±0.05	41.72 ±0.05	41.72 ±0.05	41.72 ±0.05
5-HTP	2	41.58	41.74 ±0.03	41.84 ±0.03	41.91 ±0.05	42.22 ±0.09	a42.34 ±0.05	42.29 ±0.03	42.26 ±0.04	42.23 ±0.05
Dopamine	10	41.66	41.76 ±0.05	41.85 ±0.05	41.90 ±0.05	42.08 ±0.07	42.11 ±0.07	42.18 ±0.05	b42.21 ±0.05	42.21 ±0.05

a = $P > 0.05$

b = $P > 0.05$

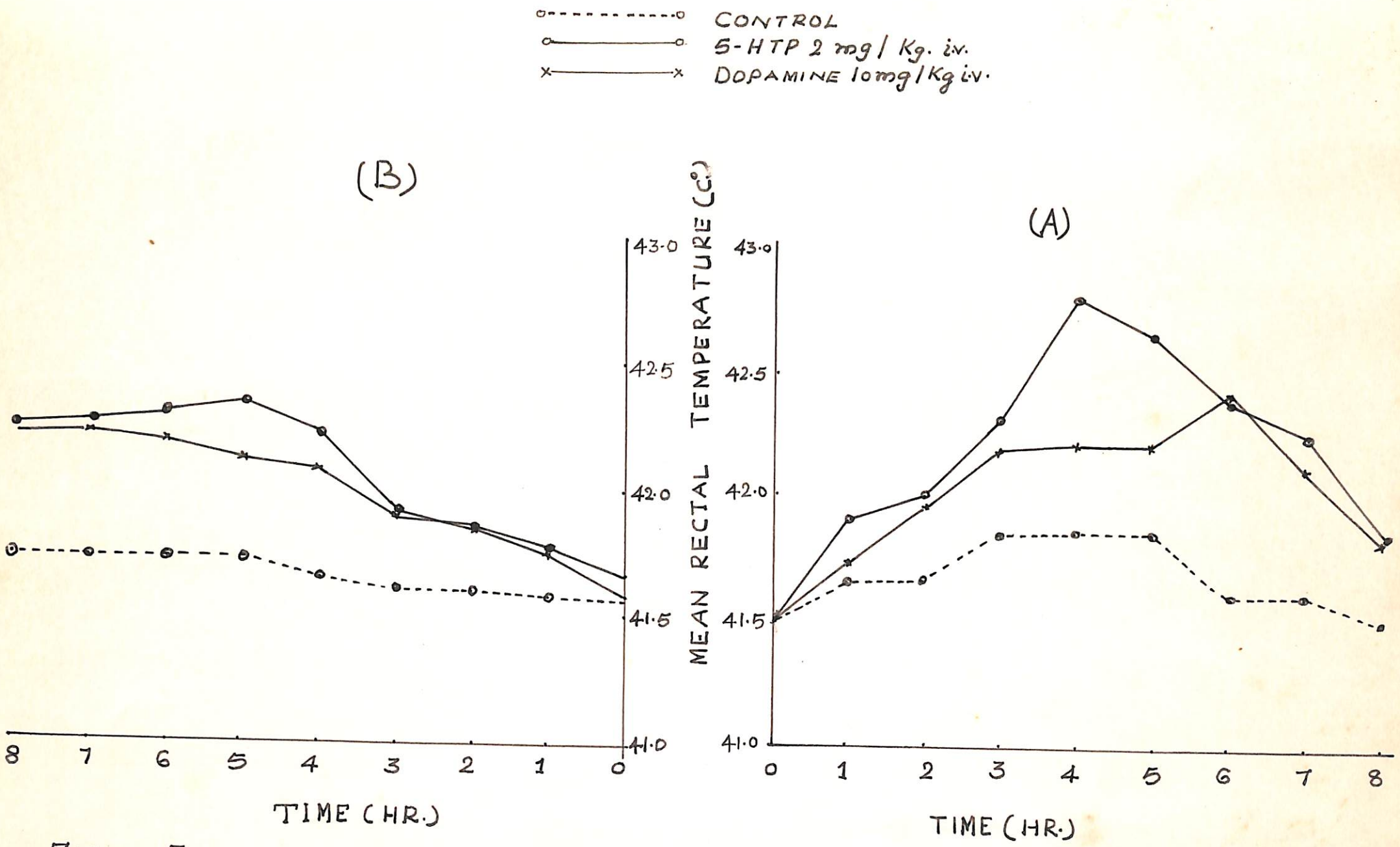


FIG. 1. EFFECT OF 5HTP AND DOPAMINE ON RECTAL TEPERATURE OF NORMAL BIRDS AT ROOM TEPERATURE 25 ± 1 C°. (A) AND 38 ± 1.5 C°. (B). EACH CURVE REPRESENTS THE MEAN RECTAL TEPERATURE CHANGES OF 15 BIRDS.

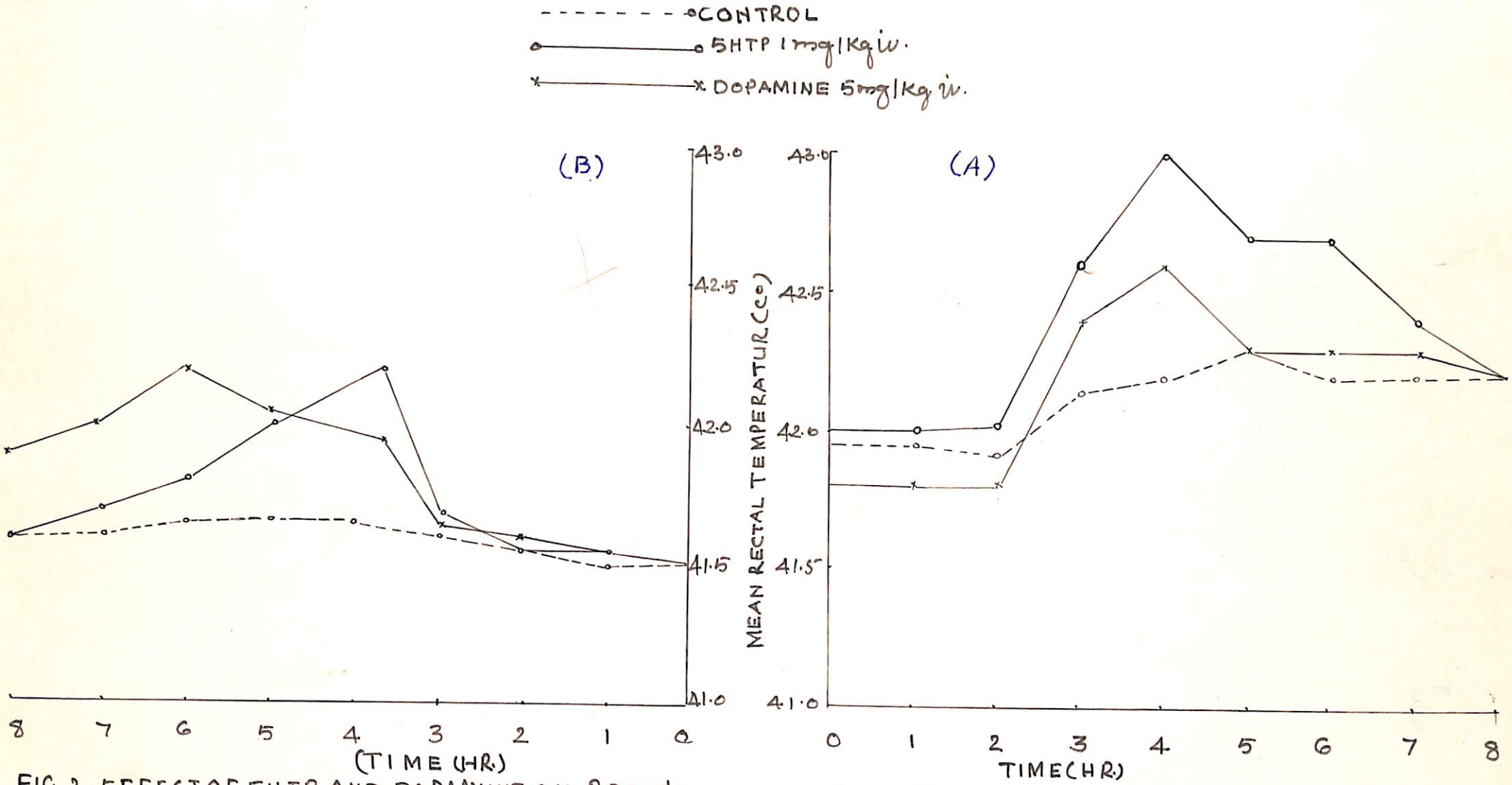


FIG. 2, EEFECT OF 5HTP AND DOPAMINE ON RECTAL TEMPERATURE OF NORMAL BIRDS AT ROOM TEMPERATURE 25±1C°. EACH CURVE REPERSENTS THE MEAN RECTAL TEMPERATURE CHANGES OF 5 BIRDS.

FIG. 3, EFFECT OF 5HTP AND DOPAMINE ON RECTAL TEMPERATURE OF BIRDS PRETREATED WITH NIALAMIDE 100mg/Kg ip. 12 HR. PRIOR, AT ROOM TEMPERATURE 25±1C°. EACH CURVE REPERSENTS THE MEAN RECTAL TEMPERATURE CHANGES OF 5 BIRDS.

nialamide 12 hour pretreated birds produced further increase in temperature which commenced after 2 hours and reached the peak level after 3 and 4 hours respectively. This rise was followed by gradual decline in body temperature extending over a period of 8 hour. The maximum increase in temperature of 0.8 ± 0.12°C and 0.9 ± 0.12°C produced by 1 mg and 2 mg/kg of 5-HTP was significant as compared to the control ($P < 0.01$).

Dopamine in doses of 5 mg and 10 mg/kg i.v.further enhanced the body temperature in nialamide pretreated birds which was similar to 5-HTP with respect to onset and duration except that latter was more hyperthermic. Maximum mean rise (0.4 ± 0.18°C) produced by 5 mg/kg of dopamine in nialamide pretreated birds was insignificant while with 10 mg/kg (0.6 ± 0.23°C) it was significant as compared to control ($P < 0.05$).

Saline treated group showed little variation in the body temperature during observation.

(b) <u>At 38 ± 1.5°C room temperature</u>

Results have been shown in Table 4 and Fig.4(B). At higher room temperature also nialamide treatment did raise the body temperature by 0.43°C but was lesser in magnitude as compared to lower room temperature.

5-HTP(2 mg/kg) and dopamine (10 mg/kg) further

TABLE 3

The effect of 5-HTP and dopamine on rectal temperature of WLH birds pretreated with nialamine 100 mg/kg (i.p.)12 hr prior at room temperature 25 ± 1°C

Drug	Dose mg/kg i.v.	Mean rectal temperature (c) with S.E.								
		0 hr	1 hr	2 hr	3 hr	4 hr	5 hr	6 hr	7 hr	8 hr
Saline	-	41.95*	41.95 ±0.04	41.90 ±0.04	42.15 ±0.04	42.20 ±0.12	42.30 ±0.12	42.20 ±0.01	42.10 ±0.08	42.10 ±0.08
5-HTP	1	42.00	42.00 ±0.00	42.10 ±0.08	42.60 ±0.08	a 43.00 ±0.02	42.70 ±0.12	42.70 ±0.12	42.40 ±0.18	42.20 ±0.12
Dopamine	5	41.80	41.80 ±0.09	41.80 ±0.09	42.40 ±0.16	b 42.60 ±0.18	42.30 ±0.12	42.30 ±0.12	42.30 ±0.12	42.20 ±0.12
Saline	-	42.10	42.00 ±0.00	42.00 ±0.00	42.00 ±0.00	42.00 ±0.00	42.30 ±0.12	42.30 ±0.12	42.00 ±0.00	41.90 ±0.11
5-HTP	2	42.30	42.30 ±0.16	42.40 ±0.18	42.60 ±0.10	42.90 ±0.10	c 43.20 ±0.12	43.20 ±0.12	43.00 ±0.10	42.50 ±0.15
Dopamine	10	42.20	42.20 ±0.12	42.20 ±0.12	42.30 ±0.12	42.50 ±0.00	d 42.90 ±0.23	42.80 ±0.25	42.50 ±0.15	42.10 ±0.08

* Figure indicates mean value of 5 birds.

a = $P < 0.01$
b = P = NS
c = $P < 0.01$
d = $P < 0.05$

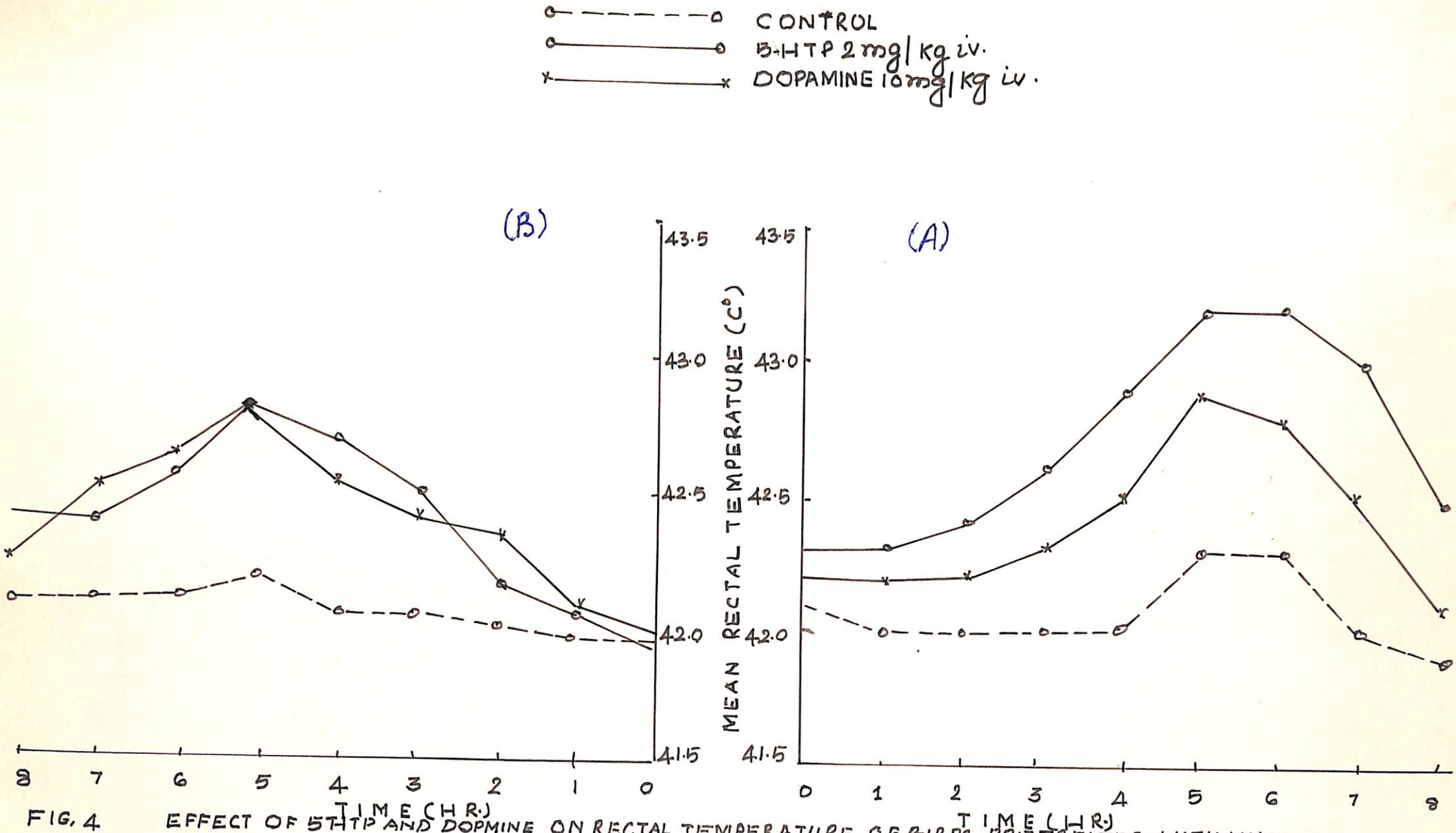


FIG. 4 EFFECT OF 5HTP AND DOPMINE ON RECTAL TEMPERATURE OF BIRDS PRE TREATED WITH NIALAMIDE 100 mg/Kg i.p. 12 HR PRIOR, AT ROOM TEPEPERATURE 25±1C° (A) AND 38±1.5C° (B) EACH CURVE REPERSENTS THE MEAN RECTAL TEMPERTURE CHANGES OF 5 BIRDS.

TABLE 4

The effect of 5-HTP and dopamine on rectal temperature of WLH birds pretreated with nialamide 100 mg/kg 12 hr prior, at room temperature 38 ± 1.5°C

Drug	Dose mg/kg i.v.	Mean rectal temperature (c) with S.E.								
		0 hr	1 hr	2 hr	3 hr	4 hr	5 hr	6 hr	7 hr	8 hr
Saline	-	*41.92	41.96 ±0.12	42.00 ±0.00	42.05 ±0.05	42.05 ±0.05	42.20 ±0.12	42.10 ±0.08	42.10 ±0.08	42.10 ±0.08
5-HTP	2	41.90	42.06 ±0.17	42.16 ±0.14	42.50 ±0.15	42.70 ±0.20	a 42.80 ±0.20	42.55 ±0.16	42.40 ±0.10	42.40 ±0.10
Dopamine	10	41.98	42.10 ±0.12	42.35 ±0.10	42.40 ±0.10	42.55 ±0.16	b 42.80 ±0.12	42.65 ±0.12	42.50 ±0.12	42.35 ±0.15

* Figure indicates the mean value of 5 birds.

a - $P < 0.05$

b - $P < 0.05$

enhanced the temperature in nialamide pretreated birds which was qualitatively similar to that observed at 25 ± 1°C except that rise with 5-HTP was of lesser degree. However, the maximum mean rise in temperature of 0.6 ± 0.2°C and 0.6 ± 0.12 produced by 5-HTP and dopamine respectively was statistically significant ($P < 0.05$).

3(A) Effect of 5-HTP and dopamine on rectal temperature of birds treated with reserpine, 48 hour prior

(a) At 25 ± 1°C room temperature

Results have been shown in Table 6 and Fig.6(A). At lower temperature reserpine 2 mg/kg i.p. produced marked fall (1.1 ± 0.05 to 1.2 ± 0.06°C) in body temperature between 1-7 hour followed by a gradual increase after 8 hours so that at 24 hour interval a mean difference of only 0.5°C was observed. The fall in temperature between 2-12 hours was highly significant ($P < 0.01$). The second injection of reserpine 2 mg/kg given at 24 hour interval produced fall but the same was of lesser magnitude than produced by the first dose (Table 5, Fig.5).

Administration of 5-HTP (2 mg/kg) in 48 hour reserpinised birds did not show any significant rise although restored the body temperature to normal which remained over 8 hour.

Dopamine (10 mg/kg on the other hand produced high rise with peak of 1.8 ± 0.1°C at 7 hour followed by

TABLE 5

The effect of reserpine (given at 0 & 24 hr) on rectal temperature of WLH birds at room temperature 25 ± 1°C & 38 ± 1.5°C

PART I

Drug	Dose mg/kg i.v.	Mean rectal temperature (c) with S.E.							
		0 hr	1 hr	2 hr	3 hr	4 hr	6 hr	8 hr	12 hr
Reserpine	2	41.5*	41.37 ±0.06	40.53 ±0.06	40.38 ±0.05	40.32 ±0.06	40.31 ±0.06	40.30 ±0.06	40.40 ±0.05
Reserpine	2	41.68	41.50 ±0.01	41.43 ±0.02	41.47 ±0.02	41.48 ±0.04	41.54 ±0.07	41.56 ±0.03	41.52 ±0.04

PART II

Drug	Dose mg/kg i.v.	Mean rectal temperature (c) with S.E.								
		24 hr	25 hr	26 hr	27 hr	28 hr	30 hr	32 hr	36 hr	48 hr
Reserpine	2	41.06 ±0.04	40.96 ±0.06	40.86 ±0.05	40.83 ±0.05	40.83 ±0.06	40.83 ±0.06	40.73 ±0.07	40.56 ±0.06	40.08 ±0.04
Reserpine	2	41.55 ±0.03	41.65 ±0.05	41.75 ±0.06	41.80 ±0.06	41.86 ±0.08	41.86 ±0.07	41.63 ±0.07	41.44 ±0.04	41.42 ±0.03

*Figure indicates the mean valueo of 15 birds.

Upper & lower figures in the table indicate the mean rectal temperature changes of 15 birds at 25 ± 1°C. and 38 ± 1.5°C respectively.

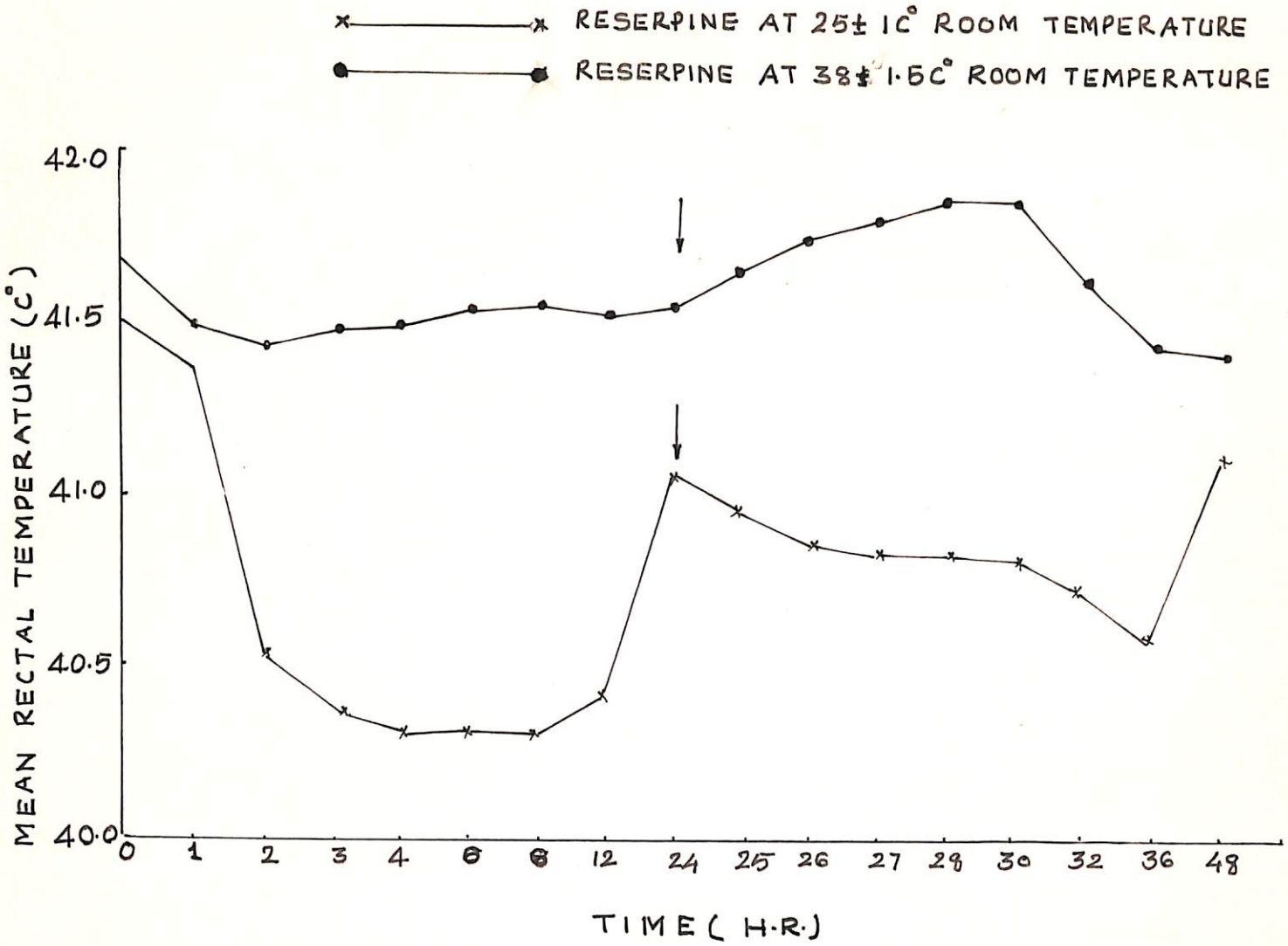


FIG. 5, EFFECT OF RESERPINE 2 mg/kg. ip (GIVEN AT 0 AND 24 HOURS) ON RECTAL TEMPERATURE OF BIRDS. EACH CURVE REPERSENTS THE MEAN RECTAL TEMPERATURE CHANGES OF 15 BIRDS. ARROW MARKS DENOTES TIME OF 2nd INJECTION.

TABLE 6

The effect of 5-HTP and dopamine on rectal temperature of WLH birds pretreated with reserpine 2 mg/kg (i.p.) 48 hr prior at room temperature 25 ± 1°C.

Drug	Dose mg/kg i.v.	Mean rectal temperature (c) with S.E.								
		0 hr	1 hr	2 hr	3 hr	4 hr	5 hr	6 hr	7 hr	8 hr
Saline	-	41.10*	41.20 ±0.09	41.20 ±0.09	41.30 ±0.09	41.30 ±0.09	41.40 ±0.06	41.40 ±0.06	41.40 ±0.06	41.40 ±0.06
5-HTP	2	41.15	41.30 ±0.09	41.30 ±0.12	41.60 ±0.10	[a] 41.60 ±0.10	41.60 ±0.10	41.60 ±0.10	41.60	41.60
Dopamine	10	41.10	41.50 ±0.00	41.50 ±0.00	41.80 ±0.12	42.00 ±0.00	42.10 ±0.08	42.60 ±0.28	[b] 43.20 ±0.10	42.90 ±0.10

* Figure indicates mean value of 5 birds.

a - $P < 0.05$

b - P = NS ? < 0.01

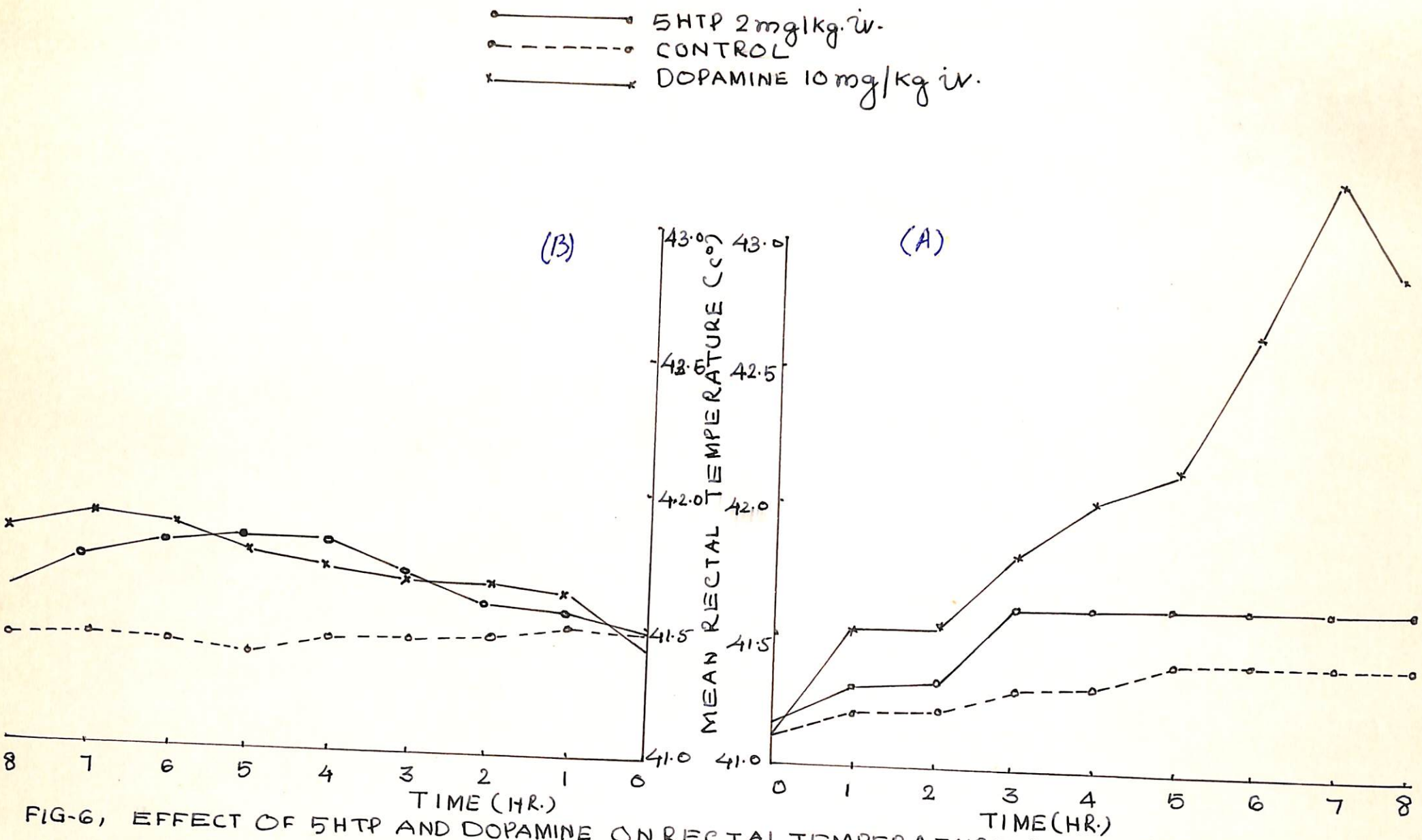


FIG-6, EFFECT OF 5HTP AND DOPAMINE ON RECTAL TEMPERATURE OF WLH BIRDS PRETREATED WITH RESERPINE 2 mg/kg. ip. 48 HR. PRIOR, AT ROOM TEMPERATURE 25±1C° (A) AND 38±1.5C°. EACH CURVE REPRESENTS THE MEAN RECTAL TEMPERATURE CHANGES OF 5 BIRDS.

slow decline extending over a period of 8 hours.

The peak rise produced by dopamine was highly significant as compared to 5-HTP response and control. ($P < 0.01$).

In control group the temperature remained subnormal even after 32 hours of 2nd injection of reserpine 2 mg/kg.

(b) <u>At 38 ± 1.5°C room temperature</u>

Results of reserpine administration are shown in Table 7 and Fig.6(B).

At higher room temperature reserpine 2 mg/kg i.p. did not produce any significant fall in body temperature. The second injection of reserpine 2 mg/kg at 24 hour instead of lowering the temperature initially produced insignificant rise (Table 5 & Fig.5).

Effect of 5-HTP (2 mg/kg) in birds pretreated with reserpine 48 hour prior, was similar with respect to onset and duration to that recorded at 25 ± 1°C except that rise peak rise (0.36 ± 0.05°C) was slightly higher and significant as compared to control ($P < 0.05$).

On the other hand marked difference in the pyretogenic response to dopamine 10 mg/kg. was recorded. Dopamine produced lesser rise (0.44 ± 0.06) at 7 hour interval which, however, was significant as compared to control ($P < 0.05$).

TABLE 7

The effect of 5-HTP and dopamine on rectal temperature of WLH birds pretreated with reserpine 2 mg/kg. (i.p.) 48 hr. Prior, at room temperature 38 ± 1°C

Drug	Dose mg/kg i.v.	Mean rectal temperature (C) with S.E.								
		0 hr	1 hr	2 hr	3 hr	4 hr	5 hr	6 hr	7 hr	8 hr
Saline	-	41.44*	41.48 ±0.04	41.44 ±0.04	41.42 ±0.06	41.42 ±0.06	41.36 ±0.01	41.40 ±0.01	41.42 ±0.06	41.40 ±0.01
5-HTP	2	41.44	41.54 ±0.07	41.56 ±0.04	41.66 ±0.08	41.78 ±0.05	a 41.78 ±0.05	41.78 ±0.09	41.72 ±0.06	41.58 ±0.07
Dopamine	10	41.42	41.60 ±0.05	41.64 ±0.06	41.64 ±0.06	41.68 ±0.07	41.74 ±0.06	41.82 ±0.06	b 41.86 ±0.06	41.80 ±0.06

*Figure indicates mean value of 5 birds.

a - $P < 0.05$

b - $P < 0.05$

(B) Effect of 5-HTP and dopamine on rectal temperature of birds treated with reserpine 1 hour prior

(b) At 25 ± 1°C room temperature

Results are shown in Table 8 and Fig.7(A).

In birds pretreated with reserpine 2 mg/kg i.p. one hour prior, administration of 5-HTP 2 mg/kg prevented the hypothermic effect of reserpine after two hour and caused maximum mean rise 1.1°C ± 0.18 at 5 hour interval which was highly significant as compared to control (reserpine treated group). ($P < 0.01$).

Dopamine 10 mg/kg also counteracted the hyperthermic effect of reserpine after a period of 3 hour and produced a peak rise of 1.2 ± 0.19°C at 5 & 6 hour interval which was highly significant ($P < 0.01$) as compared to control (reserpine treated group).

In the saline treated group temperature fall commenced gradually after two hour with a peak fall of 1°C ± 0.18 at 5 hour and sustained over a period of 8 hour.

(b) At 38 ± 1°C room temperature

Results of the administration of 5-HTP (2 mg/kg) and dopamine (10 mg/kg) are shown in the Table 9 and Fig.7 (B).

TABLE 8

The effect of 5-HTP and dopamine on rectal temperature of WLH birds pretreated with reserpine 2 mg/kg (i.p.) 1 hr prior at room temperature 25 ± 1°C

Drug	Dose mg/kg i.v.	Mean temperature (c) with S.E.								
		0 hr	1 hr	2 hr	3 hr	4 hr	5 hr	6 hr	7 hr	8 hr
Saline	-	41.55*	41.40 ±0.01	41.10 ±0.08	41.00 ±0.00	40.70 ±0.02	40.60 ±0.18	40.80 ±0.12	40.80 ±0.12	40.80 ±0.12
5-HTP	2	41.60	41.40 ±0.10	41.70 ±0.18	41.70 ±0.18	41.70 ±0.18	a 41.70 ±0.18	41.70 ±0.18	41.70 ±0.18	41.75 ±0.10
Dopamine	10	41.65	41.40 ±0.10	41.30 ±0.09	41.30 ±0.12	41.50 ±0.15	41.80 ±0.20	b 41.80 ±0.20	41.75 ±0.18	41.75 ±0.18

* Figure indicates mean value of 5 birds.

a - $P < 0.01$

b - $P < 0.01$

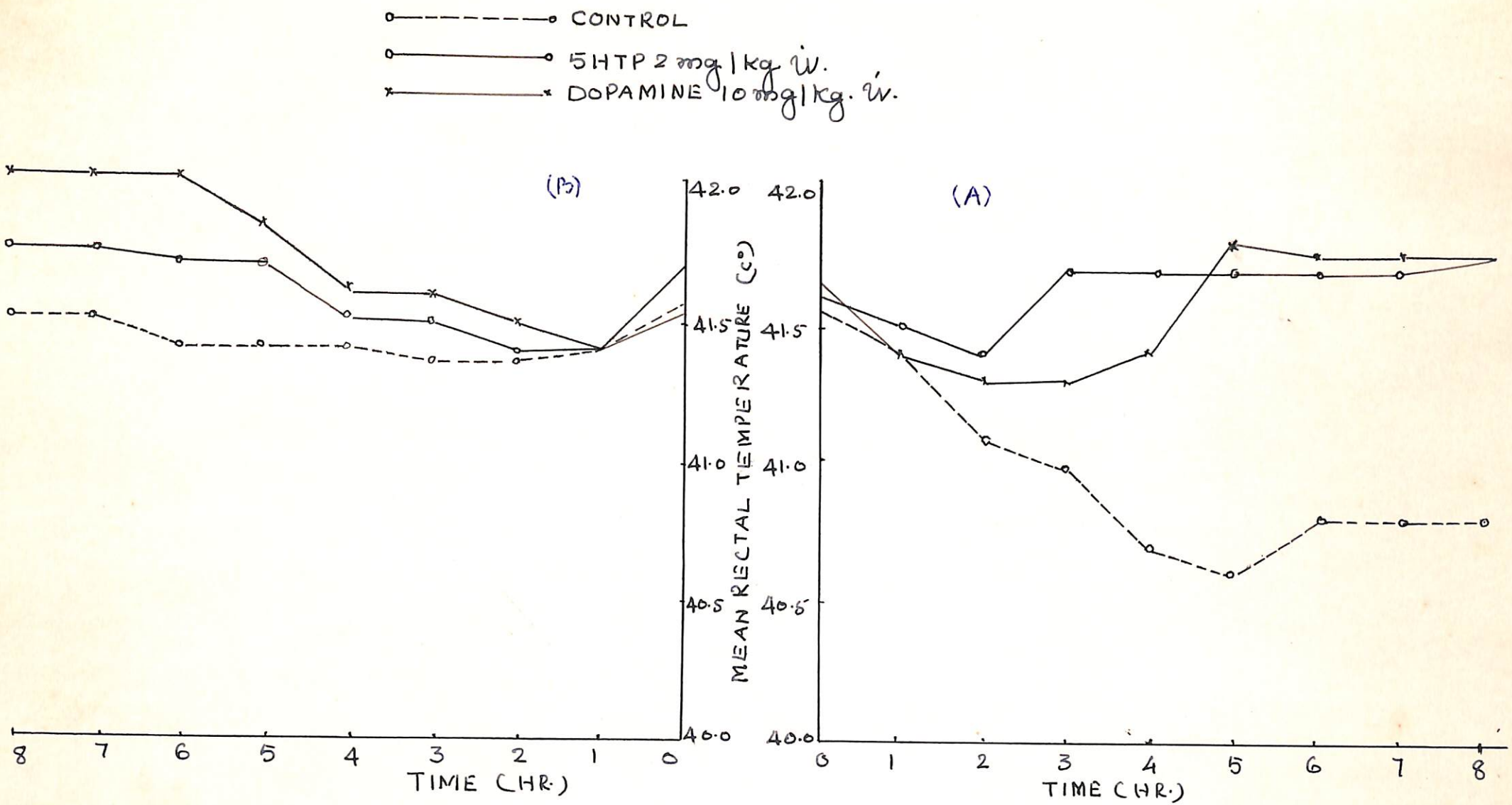


FIG. 7, EFFECT OF 5HTP AND DOPAMINE ON RECTAL TEMPERATURE OF BIRDS TREATED WITH RESERPINE 2 mg/kg. ip. 1HR. PRIOR, AT ROOM TEMPERATURE 25±1C° (A) AND 38±1.5°C° (B). EACH CURVE REPERSENTS TH MEAN RECTAL TEMPERATUR CHANGES OF 5 BIRDS.

TABLE 9

The effect of 5-HTP and dopamine on rectal temperature of W.L.H. birds pretreated with reserpine 2 mg/kg i.p. one hour prior at room temperature 37 ± 1°C

Drug	Dose mg/kg i.v.	Mean rectal temperature (c) with S.E.								
		0 hr	1 hr	2 hr	3 hr	4 hr	5 hr	6 hr	7 hr	8 hr
Saline	-	41.56*	41.40 ±0.10	41.35 ±0.11	41.35 ±0.11	41.40 ±0.10	41.40 ±0.10	41.40 ±0.00	41.50 ±0.00	41.50 ±0.00
5-HTP	2	41.54	41.40 ±0.10	41.40 ±0.10	41.50 ±0.09	41.50 ±0.00	41.70 ±0.18	41.70 ±0.18	a 41.75 ±0.11	41.75 ±0.11
Dopamine	10	41.68	41.40 ±0.10	41.50 ±0.00	41.60 ±0.00	41.60 ±0.00	41.75 ±0.21	b 42.00 ±0.09	42.00 ±0.00	42.00 ±0.00

* Figure indicates the mean value of 5 birds.

a - P = NS

b - P $<$ 0.05

At higher room temperature 5-HTP in one hour prior reserpinised birds did not show significant rise in body temperature although restored it to normal after 6 hour of its administration.

Dopamine on the other hand produced a significant rise ($P < 0.05$) at $0.6 \pm 0.00^{o}C$ at 6 hour interval which persisted beyond 8 hours.

Saline treated group showed no significant fall.

4. Effect of 5-HTP on rectal temperature of birds treated with Cyproheptadine 1 hour prior

(a) At $25 \pm 1^{o}C$ room temperature

Results are shown in Table 10 and Fig. 8(A).

Administration of 5-HTP (2 mg/kg i.v.) in Cyproheptadine pretreated birds produced a fall of $0.4 \pm 0.05^{o}C$ within one hour and then there was a gradual increase in body temperature reaching to peak level at 4 hour interval followed by a gradual decline sustaining over period of 7 hour. The peak rise produced by 5-HTP ($0.4 \pm 0.22^{o}C$) was statistically insignificant as compared to its control. The group treated with Cyproheptadine alone caused fall in temperature ($0.3 \pm 0.01^{o}C$) within two hour followed by a gradual increase reaching to its normal value at about 6 hour.

TABLE 10

The effect of 5-HTP on rectal temperature of EW.L.H. birds pretreated with cyproheptadine 2 mg/kg (i.p.) 1 hr prior at room temperature 25 ± 1°C

Drug	Mean rectal temperature (C) with S.E.								
	0 hr	1 hr	2 hr	3 hr	4 hr	5 hr	6 hr	7 hr	8 hr
NSS (i.v.)	42.00*	42.00 ±0.00	42.00 ±0.09	42.10 ±0.06	42.10 ±0.06	42.10 ±0.06	41.92 ±0.09	41.88 ±0.09	41.80 ±0.06
Cyproheptadine 2 mg/kg & NSS(i.p.)	42.00	41.70 ±0.01	41.80 ±0.05	41.80 ±0.07	41.90 ±0.08	41.96 ±0.09	41.90 ±0.08	41.90 ±0.08	41.90 ±0.08
5-HTP 2 mg/kg(i.v.) & cyproheptadine.	42.00	41.60 ±0.05	41.70 ±0.11	41.90 ±0.18	a 42.50 ±0.22	42.41 ±0.19	42.21 ±0.13	42.16 ±0.06	41.96 ±0.09

* Figure indicates the mean value of 5 birds.

a - P = NS

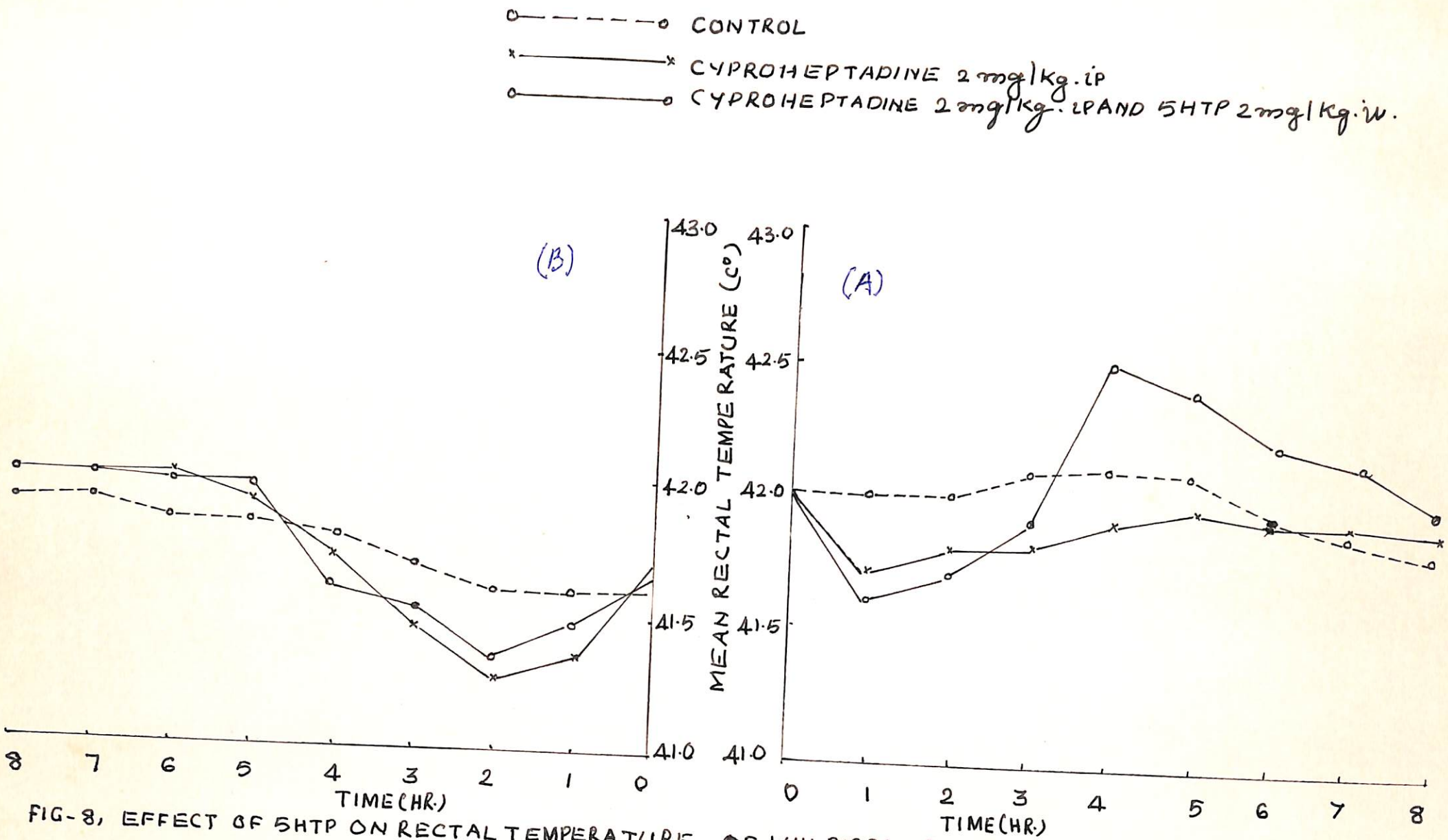


FIG-8, EFFECT OF 5HTP ON RECTAL TEMPERATURE OF WLH BIRDS TREATED WITH CYPROHETADINE ONE HR. PRIOR, AT ROOM TEMPERATURE OF 25± 1C° (A) AND 38± 1.5C° (B) EACH CURVE REPRESENTS THE MEAN RECTAL TEMPERATURE CHANGES OF 5 BIRDS.

(b) At 38 ± 1.5°C room temperature

Results are shown in Table 11 and represented in Fig. 8(B).

5-HTP at higher temperature also did not show any significant rise in temperature. The effect of Cyproheptadine was the same as recorded at 25 ± 1°C.

5. Effect of dopamine on rectal temperature of birds treated with Yohimbine one hour prior

(a) At 25 ± 1°C room temperature

Results are summarised in Table 12 and shown in Fig.9(A).

Effect of dopamine (10 mg/kg) in Yohimbine (2 mg/kg i.p.) pretreated birds showed the response as in normal birds described earlier. Yohimbine had no significant effect on the body temperature.

(b) At 38 ± 1.5°C room temperature

Results are shown in Table 13 and Fig.9(B).

Effect of dopamine at higher room temperature was the same as observed at lower room temperature. Yohimbine was also found to be ineffective.

TABLE 11

The effect of 5-HTP on rectal temperature W.L.H.birds pretreated with Cyproheptadine 2 mg/kg (i.p.) one hr prior at the room temperature 37 ± 1 °C

Drug	Mean rectal temperature (c) with S.E.								
	0 hr	1 hr	2 hr	3 hr	4 hr	5 hr	6 hr	7 hr	8 hr
Only NSS(i.v.)	41.6*	41.60 ±0.00	41.60 ±0.00	41.70 ±0.04	41.80 -	41.84 41.96 ±0.03	41.84 ±0.03	41.92 ±0.10	41.92 ±0.10
Cyproheptadine 2 mg/kg & NSS(i.p.)	41.70	41.34 ±0.08	41.26 ±0.07	41.46 ±0.07	41.70 ±0.18	41.92 ±0.10	42.00 ±0.00	42.00 ±0.00	42.00 ±0.12
5-HTP 2 mg/kg(i.v.) plus Cyproheptadine	41.66	41.48 ±0.04	41.34 ±0.13	41.52 ±0.12	41.60 ±0.14	41.96 ±0.14	41.98 ±0.12	a 42.00 ±0.00	42.00 ±0.00

* Figure indicates mean value of 5 birds.

a - P = NS

TABLE 12

The effect of dipamine on rectal temperature of W.L.H. birds pretreated with Yohimbine 2 mg/kg (i.p.) 1 hr prior, at room temperature 25 ± 1 °C

Drug	Mean rectal temperature (c) with S.E.								
	0 hr	1 hr	2 hr	3 hr	4 hr	5 hr	6 hr	7 hr	8 hr
Only NSS (i.p.)	41.90*	41.90 ±0.08	42.10 ±0.06	42.10 ±0.06	42.00 ±0.10	42.00 ±0.10	41.90 ±0.12	41.86 ±0.10	41.80 ±0.11
Yohimbine 2 mg/kg NSS (i.p.)	42.00	42.00 ±0.12	42.14 ±0.13	42.14 ±0.13	42.15 ±0.05	42.00 ±0.12	41.80 ±0.10	41.70 ±0.07	41.65 ±0.07
Dopamine 10 mg/kg (i.v.) & Yohimbine (i.p.)	41.90	42.00 ±0.12	42.46 ±0.12	42.60 ±0.08	a 42.66 ±0.12	42.37 ±0.13	42.00 ±0.19	42.00 ±0.09	41.90 ±0.10

* Figure indicates the mean value of 5 birds.

a - $P < 0.05$

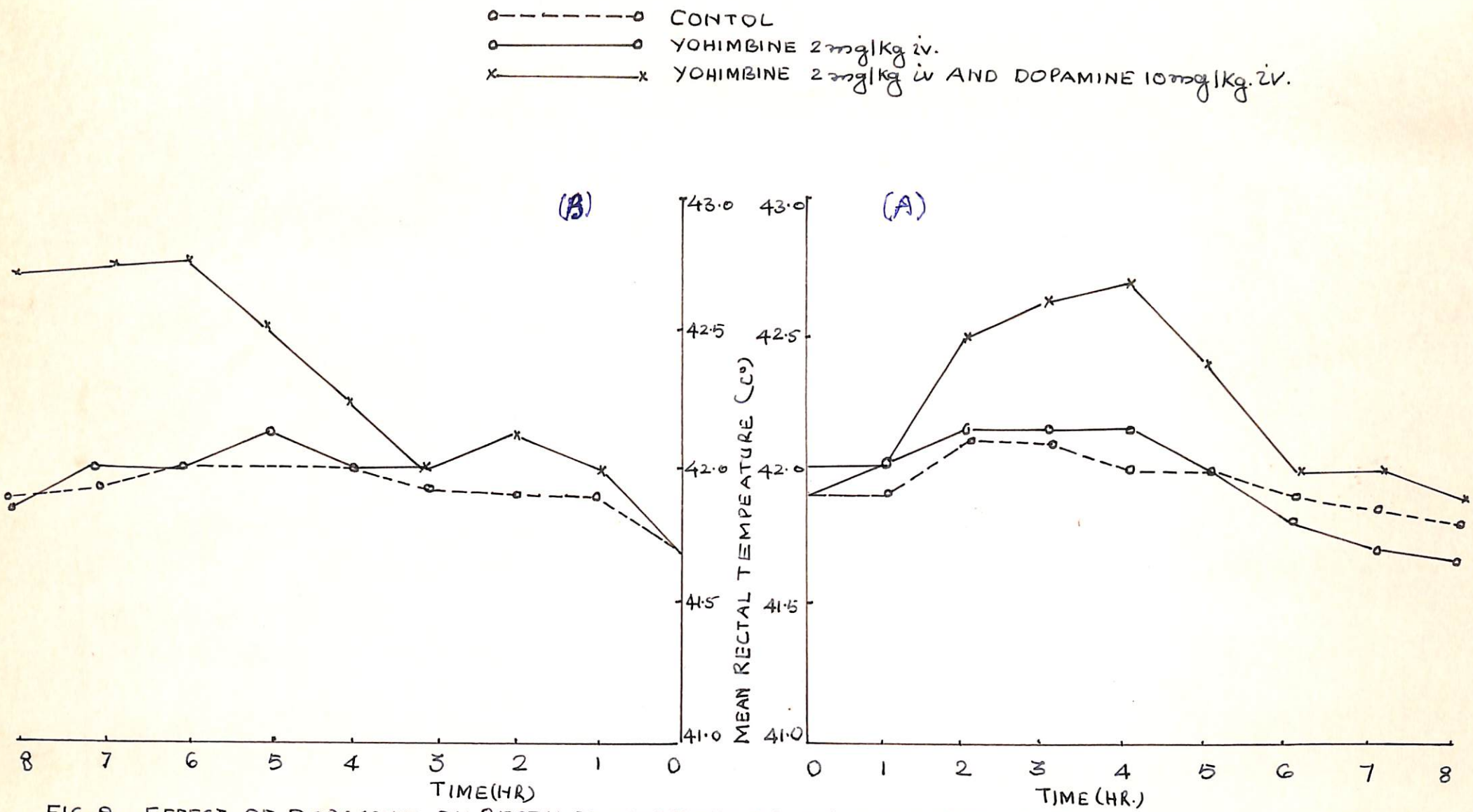


FIG. 9, EFFECT OF DOPAMINE ON RECTAL TEMPERATURE OF BIRDS TREATED WITH YOHIMBINE ONE HR. PRIOR, AT ROOM TEMPERATURE 25 ± 1C° (A) AND 38 ± 1·5C° (B) EACH CURVE REPERSENTS THE MEAN TEMPERATURE CHANGE OF 5 BIRDS.

TABLE 13

The effect of dopamine on rectal temperature of W.L.H. birds pretreated with Yohimbine 2 mg/kg (i.p.) 1 hr prior at room temperature 38 ± 1.5°C

Drug	Mean rectal temperature (c) with S.E.								
	0 hr	1 hr	2 hr	3 hr	4 hr	5 hr	6 hr	7 hr	8 hr
Only NSS	41.70*	41.90 ±0.08	41.90 ±0.08	41.92 ±0.09	42.00 ±0.00	42.00 ±0.00	42.00 ±0.00	41.92 ±0.09	41.86 ±0.04
Yohimbine 2 mg/kg & NSS (i.p.)	41.70	42.00 ±0.00	42.00 ±0.00	42.00 ±0.00	42.00 ±0.00	42.12 ±0.01	42.00 ±0.00	42.00 ±0.00	41.84 ±0.44
Dopamine 10 mg/kg (i.v.) & Yohimbine (i.p.)	41.70	42.00 ±0.00	42.10 ±0.06	42.00 ±1.12	42.22 ±0.13	42.56 ±0.01	a 42.76 ±0.08	42.74 ±0.12	42.70 ±0.07

*Figure indicates the mean value of 5 birds.

a - $P < 0.05$

Gross observational effects

While studying the effect of 5-HTP and dopamine on rectal temperature of normal, nialamide, cyproheptadine and Yohimbine pretreated birds, their gross observational effects were also studied.

5-HTP and dopamine in normal birds did not show any marked gross observational effects.

However, in birds pretreated with reserpine 2 mg/kg i.p. one hour prior, these two agents reduced the degree of sedation and dopamine was found more potent than 5-HTP in inhibiting the sedative effects of reserpine.

In 48 hours reserpinised birds with reinforcement at 24 hour, degree of sedation was reduced markedly following 5-HTP and dopamine administration and after a lapse of 3-4 hours birds were quite active, ate and walked well in the cage.

Reserpine (2 mg/kg i.p.) by itself initially showed very mild degree of stimulation characterised by increase in spontaneous cry and spontaneous motor activity followed by depression. Sedation in birds commenced after half hour, reached the peak level in two hour and continued as such for 10 hours followed by eventual return to normal over a 24 hour period. During the peak sedation cataleptic effects characterised by muscular rigidity and immobility

of body and limbs were observed. When birds were kept in awkward position they remained immobile for few minutes. The birds became more passive and showed bilateral ptosis.

Birds either sitting or standing were observed motionless in the cage, and when taken out immediately dropped down. During peak sedative effects birds showed least responsiveness to handling and mildly reacted to sensory and auditony stimuli.

Peripheral cholinergic signs such as diarrhoea and salivation were also observed. Nasal and eye secretions were not markedly increased. Few birds showed marked panting (respiration with open beak).

With second injection of reserpine (2 mg/kg i.p.) given at 24 hour interval sedation and adynamic signs reappeared with shorter latency of 15-20 minutes which reached the peak level within one hour and same set of signs was observed as with that of first injection.

In nialamide pretreated birds, 5-HTP and dopamine showed stimulant signs and nialamide alone did not show any marked gross observational effects.

5-HTP in cyproheptadine treated birds showed initially sedation which passed off after a lapse of 3-4 hours. Cyproheptadine alone, showed some signs of sedation between 1-5 hours.

B. EFFECT OF 5-HTP AND DOPAMINE ON BLOOD PRESSURE OF ANAESTHETISED BIRDS

Effects of 5-HTP, 5-HT and cyproheptadine on the blood pressure of the fowl have been shown in Fig. 10.

Intravenous administration of 5-hydroxytyptophan (0.5 mg/kg) in anaesthetised birds produced initially transitory rise followed by biphasic decrease in blood pressure. The depressor phase was then succeeded by a marked pressor phase with rapid decline to an extent of 75 per cent of the rise, complete recovery occurred in half an hour. With smaller doses (5-50 mcg/kg) of 5-HTP only pressor response was observed.

5-hydroxytryptamine (10 mcg/kg) showed depressor response. However, the effect of 5-HT in some cases showed a triphasic response - a depressor phase following injection; a succeeding pressor phase and finally, within one minute of the injection, a prolonged depressor phase. Blood pressure response to 5-HTP and 5-HT was markedly antagonised by cyproheptadine (0.7 mg/kg). This agent per se produced a depressor response.

Effects of epinephrine dopamine and yohimbine have been shown in Fig.11. Both dopamine (.05 mg/kg) and epinephrine (2.5 mcg/kg) showed a pressor response. Unlike epinephrine the action of dopamine was less marked but

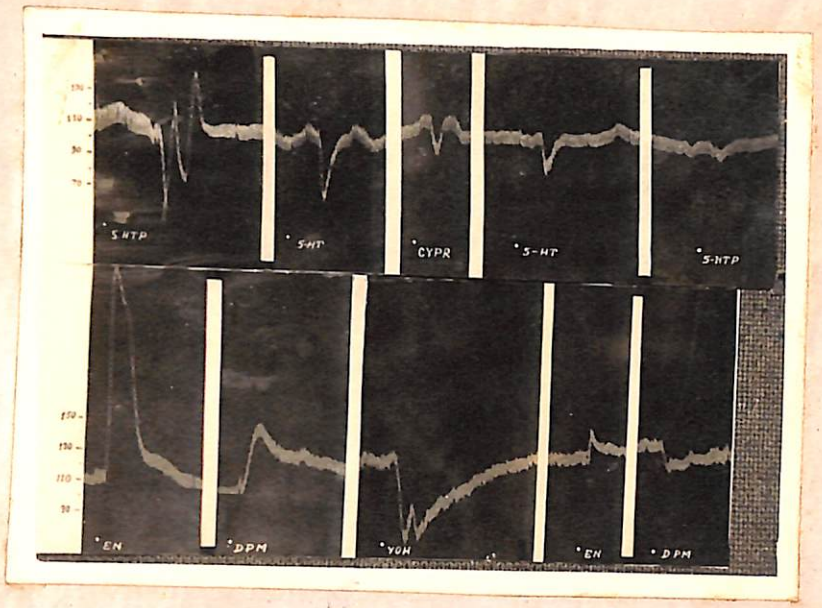


Fig.10 (Upper)

Shows the effect of 5-hydroxytryptophan (5-HTP), 0.5 mg/kg.. and 5-hydroxytryptamine (5-HT), 10 mcg/kg. before & after cyproheptadine (CYPR), 0.7 mg/kg. on the blood pressure of anaesthetised W.L.H. birds.

Fig.11 (Lower)

Shows the effect of epinephrine (EN), 2.5 mcg/kg. & dopamine (DPM), 0.05 mcg/kg. before and after yohimbine (YOH), 0.5 mg/kg. on the blood pressure of anaethetised W.L.H.birds.

CHAPTER V

DISCUSSION

DISCUSSION

Present studies with 5-HTP and dopamine on body temperature and gross effects in W.L.H. birds indicate that both 5-HTP and dopamine have hyperthermic response. Nialamide pretreatment enhances the hyperthermic response to 5-HTP and dopamine. Reserpine produces marked hypothermia at lower room temperature but fails to do so at higher one. 5-hydroxytroptophan in reserpine pretreated birds restores the body temperature to normal, dopamine, on the other hand, produces significant rise which is more marked at lower room temperature that at higher one.

Cyproheptadine (anti-5-HT) produces fall in rectal temperature within one hour which returns to normal within 4-5 hours. 5-HTP in cyproheptadine pretreated birds produces rise in temperature at usual interval of 4 hour through initially its action is reversed by its antagonist.

Yohimbine neither seems to have any significant effect on body temperature nor it modifies the hyperthermic response to dopamine.

The hyperthermic response to 5-HTP and dopamine seems to be influenced by ambient temperatures. At higher ambient temperatures response to these compounds

is lesser in magnitude but of prolonged duration as compared to their effect at lower room temperature.

5-HTP and dopamine do not produce marked gross observable effect in normal birds. In reserpine pretreated birds these two agents reduce the degree of sedation. However, dopamine was more active. In nialamide pretreated birds 5-HTP and dopamine show some signs of stimulation whereas nialamide alone does not show any marked gross observable effects. 5-HTP in cyproheptadine pretreated birds, show initially sedation which passes off later. Cyproheptadine alone produces sedative effects between 1-5 hours.

Response to 5-HTP is presumed to be mediated by serotonin formed from injected 5-HTP (Bogdanski et al, 1958). The fact that nialamide (MAO inhibitor) enhances the pyretogenic response to 5-HTP also supports this assumption since, 5-HT is deaminated by this enzyme. Further findings of Udenfriend et al. (1957a) and Segawa (1970) indicate that 5-HTP readily pass the BBB in contrast to 5-HT and raises the level of this amine in the brain. 5-hydroxytryptamine being a highly polar substance fails to pass the BBB and increase its level in the brain. According to these workers, serotonin formation proceeds at rapid rate in the brain and other

tissues after the administration of 5-HTP. The rate of serotonin formation as found by these workers corresponds well with the onset of the pyretogenic effect of 5-HTP. As reported by Bogdanski et al, (1958), increase in the serotonin level in different parts of the brain after 5-HTP depends upon the degree of 'L-amino acid decarboxylase' activity and since the 'decarboxylase' activity in the avian diencephalon is the highest (Aprison et al, 1964), it is likely that marked increase in serotonin level may have resulted after 5-HTP administration.

Hyperthermic response to i.v. 5-HTP in birds observed in the present study is similar to that recorded with i.c.v. administration of this agent in dogs and monkeys (Feldberg et al, 1967) and in cats (Hawary & Feldberg, 1967). The rise in temperature in dogs and monkeys was associated with increased output of 5-HT in the effluent from perfused 3rd ventricle, as observed by Feldberg and his colleagues. Horita & Gogerty (1958) have also reported the hyperthermic response in rabbits after administration of i.v. 5-HTP. As described by Hodge et al. (1964) tryptophan and hydroxylated tryptophan in MAO inhibitor pretreated guinea pigs produced a pyretogenic response but when their conversion to serotonin was blocked by 'decarboxylase' inhibitor, these agents failed to elicit such

response in MAO inhibitor treated animals. Giarman et al, (1968) similarly found additive pyretogenic response associated with 80 per cent increase in the hypothalamic serotonin in the rabbit when 5-HTP was coadministered with bacterial pyrogen. Thus the result of the present investigation and those of others as discussed above clearly indicate that 5-HTP action is mediated by 5-HT formed from 5-HTP after its administration.

Central action of 5-HTP with respect to hypertermic response in birds may be explained in the light of the following evidences -

1. The response to 5-HTP is independent of environmental temperature.

2. Large dose of 5-HT when administered i.v. in the chicken, does not produce rise in rectal temperature rather opposite response is obtained (Allen & Marley, 1966-67). In the pigeon 5-HT injected subcutaneously produces hypothermic response (Hoffman, 1958).

3. Imperfect or nonexistence of BBB in chicks under 3 weeks of age has been described by Dewhurst & Marley (1965) and in 1-21 days chicks pretreated with mebanazine (MAO inhibitor) 5-HT invariably gives a hyperthermic response. However, the hyperthermic response to 5-HTP

in adult birds, though unlikely resulting from an action of 5-HTP at synapses situated more caudally in the brain stem regions other than the hypothalamus may not be excluded.

The hypothermic response to i.p. cyproheptadine is similar to that as recorded by Canal & Ornesi (1961b) in rabbit.

L-dopa (Precursor of catecholamines) similar to 5-HTP in mammals penetrates the BBB readily in the pigeons (Jurio & Vogt 1967). With heavy doses of dopamine (immediate precursor of NE & EN), some amount may be expected to pass the BBB and thus to increase the level of amines in the brain. Dopamine is found in higher concentrations in the avian brain (Jurio & Vogt, 1967), where it is converted to NE & EN by the enzyme 'dopamine-B-oxidase' and 'phenyl-ethanol amine N-methyl transferase' respectively and its action in presumed to be mediated by formed NE & EN. The experimental finding in rabbit by Giarman et al, (1968) that dopa when coadministered with bacterial pyrogen produces hyperthermia with concomitant increase in hypothalamus NE level to an extent of 75 per cent does suggest that action of dopa and dopamine is mediated by NE. Present finding in normal birds with dopamine corresponds with

that obtained in hedgehog by Uusapaa (1963a,b) after subcutaneous administrations of dopa and dopamine.

To see whether the action of dopamine is mediated centrally and by NE & EN its effect on Yohimbine (an α -adrenergic blocking agent) pretreated birds has been observed. Yohimbine having marked peripheral vasodilator action has failed to counteract the hyperthermic response to dopamine indicating that the action of dopamine is probably of central origin.

Alteration in body temperature brought about by peripheral action of i.v. NE & EN similar to 5-HT depends upon the environmental temperatures with heat loss predominating below and heat gain predominating above the zone of thermal neutrality. Since, dopamine in fowl elicits rise both at lower and higher ambient temperatures further suggest its central action. However, hyperthermic response to dopamine on account of its action at synapses situated more caudally in the brain stem regions may not be excluded.

The effect of NE & EN on the rectal temperature of the adult chicken is inconsistent whereas in 1-21 days old chicks they produce hypothermic response associated with poikilothermia (Allen & Marley, 1966-67). These experimental findings suggest that the response to dopamine is of peripheral origin. Since, the effect

of NE & EN in adult birds is inconsistent (that is in some cases rise and in other cases ineffective or even fall in rectal temperature) and as in young chicks the temperature control system is not fully developed, until down feathers are replaced by juvenile plumage after three weeks of age (Moreng & Shaffner, 1951), the possibility that pyretogenic response to dopamine is centrally mediated may not be ignored.

In the chicken nialamide produces hyperthermic response which may be best explained as being due to inhibition of MAO in the avian hypothalamus. The hyperthermic response to nialamide in birds is similar to that observed in cats and dogs with i.p.tranylcypromine (Feldberg & Lotti, 1967,a,b) and in rabbits obtained with pheniprazine on systemic administration (Des Prez et al, and Shellenberger, 1966).

The enhancement of the pyretogenic response to nialamide by 5-HTP in birds is similar to that obtained in rabbits by Horita & Gogerty (1958) and Des Prez et al, (1966) on systemic administration of iproniazid.

The enhancement of the pyretogenic response by dopamine in MAO inhibitor pretreated birds is in agreement with the results obtained with dopa in rabbits (Kroneberg & Kurbjuweit, 1959) and in rats pretreated

with iproniazid and high spinal cord transection (Mantegazza, 1964).

In order to see whether the pyretogenic response to 5-HTP and dopamine is mediated by 5-HT and NE & EN their effects on 1 and 48 hours reserpinised birds have been observed. Reserpine is known to deplete the monoamines from avian brain (Jurio & Vogt, 1967). As reported by these workers a dose of 1 mg/kg of reserpine given by systemic route depleted NE to an extent of 86 per cent within 3 days with slow return to normal level and was not quite complete before 19 days. With same dose of reserpine on the other hand the concentration of 5-HT was reduced markedly within one hour and the maximum depletion was achieved just after 2 hours of the reserpine administration. Depletion lasted at least 11 days and disappeared completely on 19th day.

In 48 hours reserpinised birds both 5-HTP and dopamine produce rise in body temperature suggesting that 5-HT and NE respectively are the agents responsible for pyretogenic response to 5-HTP and dopamine. The reversal of reserpine hypothermia by these two agents also supports the similar view. The higher rise in body temperature produced by dopamine in reserpinised birds is in rapport with the fact that the depletion of catecholamines by reserpine is a delayed process as

reported by Jurio & Vogt (1967) or may be due to the tissue hypersensitivity mechanism.

Reserpine causes depletion of 5-HT and catecholamines by impairing their storage mechanism. Segawa (1970) reported that reserpine inhibited the increase in the 5-HT concentrations in the neuronal cells particularly in the synaptic vesicles after 5-HTP administration in the rabbit, yet more than endogenous amounts of 5-HT were detected. This indicates that at least part of 5-HTP penetrates into the neuronalcells and is converted to 5-HT even after reserpine. Further these workers found that reserpine selectively block the mechanism for incorporating 5-HT into the synaptic vesicles. The above mechanism observed by these workers may also be held true in case of catecholamines as well.

Experimental findings that 5-HTP and dopamine produce greater response with comparatively rapid onset and of lesser duration at lower than at higher ambient temperatures may presumably be due to the fact that at higher ambient temperatures inflow from the peripheral receptors modifies in some way the centrally initiated process. Similarly, the difference with respect to onset and duration of action of these two agents may be due to difference in the rate of enzymatic synthesis

and inactivation between 5-HT and NE & EN formed from 5-HTP and dopamine. The comparatively delayed onset and prolonged duration of response to dopamine suggests its slow conversion and turnover to acid metabiolites.

Present gross observational studies also support the view that the response to 5-HTP and dopamine is mediated by 5-HT and NE & EN respectively. In reserpinised birds both 5-HTP and dopamine reduce but not abolish the sedative effects induced by reserpine supports the above hypothesis. Failure to obtain complete reserpine reversal with 5-HTP may probably be related to the release of NE by reserpine (Shore et al, 1957). Similarly, dopamine, though comparatively more potent than 5-HTP fails to counteract completely the sedative effects induced by reserpine. These explain that both 5-HT and NE are depleted by reserpine. The gross observational effects produced with 5-HTP and dopamine in reserpinised birds is similar to that observed in rats by Carlsson et al, (1957). The sedative effects produced by cyproheptadine may be due to its antiserotonin activity.

Results of the present investigation on fowl also furnish the evidence that physiological control of body temperature requires the participation of

central biogenic amines as proposed by Feldberg et al. (1963, 1964a).

If pharmacological results obtained with biogenic amines in different species indicate their transmitter functions, it will follow that in cats, dogs, monkeys, rats and mice, these functions are mediated by catecholamines and 5-HT (Feldberg et al, 1963, 1967 & 1967b and Brittain & Handley, 1967), in rabbits and sheep mainly by catecholamines (Cooper et al, 1965; and Bligh, 1966) and in oxen, goats by 5-HT alone (Findley & Robertshaw, 1967 and Anderson et al, 1966). Further that same biogenic amine may be used in one species as central transmitter for raising and in other for lowering body temperature. Also that in some species one amine is hypo or hyperthermic and other amine has reciprocal role to play. Besides, both 5-HT and catecholamines in the same species may have one type of either heat gain or heat loss hypothalamic neurotransmitter role as has been reported in rats and mice. In the present investigations on chickens where both amines seem to play similar type of heat gain neurotransmitter role is in accord with that obtained in rats and mice in which both amines (5-HT and catecholamines) are mainly hypothermic. However, it remains to be seen though

unlikely, whether some substances other than 5-HT and catecholamine are involved to play heat loss neurotransmitter role in thermoregulation in chickens.

Based on various studies as reported by several workers, it seems apparent that a marked species variation in respect to the neurotransmitter functions of 5-HT and catecholamines in physiological control of body temperature is existing. Other such species variation as adrenergic innervations of sweat glands in horse and sheep and cholinergic innervations of sweat glands in others is well known.

Since, in chickens catecholamines and 5-HT seem to play hyperthermic neurotransmitter role it will follow that a constant or a near constant body temperature in this species is maintained by a continuous release of 5-HT and catecholamines in optimal concentrations. Changes in body temperature will be then expected to be brought about by an inhibition or augumentation in the release of solitary or both the amines concomittantly. Fall in temperature may, therefore, be visualised as being due to inhibition in the release 5-HT and/or catecholamines. Conversely, a rise in body temperature may be expected due to an augumentation in the release of 5-HT and/or catecholamines.

Based on present findings the fever produced by bacterial pyrogens in the fowl, i.e.the fever of

infectious disease may be explained. According to the views of Bennett & Beeson (1953) and Atkins (1960), the bacterial pyrogens themselves are not the ultimate pyretogenic agent; it is derived from the white cells in the host on which bacterial pyrogens act. There is good evidence that leucocyte pyrogen produced in this way acts on the hypothalamus to produce fever. If we take the view of Kronerberg & Kurbjuweit (1959) as well as of Going (1959) and Des Prez et al, (1966) that monoamines are the mediator of fever of bacterial origin, the rise in body temperature produced by bacterial pyrogen in infectious diseases of chickens may be visualised to be brought about by similar mechanism mentioned above. In addition pyrogens may render the hypothalamus more sensitive to the action of 5-HT and catecholamines and there may be further possibility that pyrogens do not act solely through the release of hypothalamic, monoamines but mimic the effect of 5-HT and catecholamines.

Alteration in body temperature induced by agents other than bacterial pyrogen in chickens may also be explained in the light of present experiments on similar line. For example, antipyretics which lower the temperature in fever induced by bacterial pyrogens but do not lower normal temperature. On the assumption that bacterial pyrogens act by initiating the release of 5-HT and/or catecholamines and by rendering the appropriate

diencephalic structures hypersensitive to these amines, the action of antipyretics will be to reverse the changes and no effect on normal temperature will be expected.

The findings that 5-HTP in small doses had a pressor and in higher a combination of pressor-depressor response, suggest that 5-HTP action is mediated by 5-HT and may have also a central component of action. 5-hydroxytryptamine in some cases showed a triphasic response. The initial fall in B.P. induced by this agent may be due to the coronary chemoreflex as in mammals (Douglas, 1965) but this needs confirmation. Small rise following a fall in the blood pressure may probably be due to increased cardiac output and peripheral vasoconstriction. The prolonged fall in blood pressure may be attributed to the inhibition of the neurogenic vasoconstriction. The variability in 5-HT action as described by Douglas (1965) may be attributable in large part to two factors. (1) 5-hydroxytryptamine action is reflexly mediated and hence, subject to influences such as pattern of innervation, route and speed of injections, anaesthetic state and spontaneous tone; and (2) tachyphylaxis is common when tests are made at frequent intervals.

Cardiovascular effects of dopamine in anaesthetised fowl indicated that this amine had effects varying

from pressor-depressor action at lower dose level to only pressor action at higher dose level. The depressor action shown by dopamine in mammals does not appear to be related to release of histamine, a histamine like effect, autonomic ganglion depression, stimulation of atropine-sensitive vasodilator nerves or combination with beta-receptors (McDonald & Goldberg, 1963). The depressor response to dopamine as suggested by these workers results from reflex dilation of limb blood vessels or due to a CNS effect. Another possible mechanism of depressor response to dopamine has been advanced by Burn & Rand (1958). These workers postulates that dopamine depressor response is due to its combination with receptors ordinarily occupied by more potent vasoconstrictor-norepinephrine. According to Eble et al. (1964), the blood pressure response to dopamine is largely the result of balance between visceral blood vessels dilation and peripheral constrictor effects. With smaller doses the visceral vasodilator effect predominate resulting into depressor response and with large doses peripheral constrictor effects predominate leading to pressor response. The above explanation may also be applicable in case of birds.

Failure to show significant blockade to epinephrine-pressor response by conventional dose of phentolamine in birds may be due to an excessive enzyme

activity concerned with inactivation of this agent or may be due to the existence of atypical α-adrenergic receptors in fowl.

The fact that yohimbine blocked significantly the pressor response to dopamine and epinephrine may be through a nonspecific other than α-adrenergic blocking action.

Pronethalol (beta-adrenergic blocking agent) produced precipitus fall in blood pressure after yohimbine may be due to myocardial depression.

MAO inhibitors cause fall in the blood pressure - a result resembling that produced by sympathetic blockade (Gessa et al, 1963). But the finding that 12 hours prior treatment of nialamide (MAO inhibitor) enhanced the response to 5-HT, epinephrine and their precursor is obviously due to an increase in the level of these amines.

CHAPTER VI

SUMMARY AND CONCLUSIONS

SUMMARY AND CONCLUSIONS

In the present investigations effects of intravenous administration of 5-hydroxytryptophan and dopamine on the body temperature of W.L.H. birds have been studied at room temperature 25 ± 1°C and 38 ± 1.5°C. Effects of these compounds have been recorded in normal, reserpine (amine depletor), nialamide (MAO inhibitor), cyproheptadine (anti-5-HT) and yohimbine (α -adrenergic blocking agent) pretreated birds. Results of the investigations are as follows :-

1. Both 5-HTP (1-2 mg/kg) and dopamine (5-10 mg/kg) had hyperthermic response but 5-HTP was more potent than dopamine. The hyperthermic response seems to be dose-dependent and is subject to the influence by environmental temperatures. 5-hydroxytryptophan and dopamine produced greater response with comparatively rapid onset and of lesser duration at lower than at higher room temperature. This indicates that at higher room temperature inflow from the peripheral receptors modifies in some way the centrally initiated process. Similarly, the difference with respect to onset and duration of the action of these two agents appears to be due to difference in the rate of enzymatic synthesis and inactivation between 5-HT and NE & EN formed from 5-HTP and dopamine. The comparatively delayed and prolonged duration of response to dopamine

suggests its slow conversion and turnover.

2. Hyperthermic response to nialamide was greater at lower than at higher room temperature and the degree of enhancement of nialamide response by 5-HTP and dopamine showed inverse relationship. The fact that 5-HTP enhanced markedly the hyperthermic response to nialamide, suggests that 5-HTP action is mediated by 5-HT since, 5-HT is deaminated by MAO.

3. Reserpine (2 mg/kg i.p.) produced marked hypothermia at lower room temperature but failed to do so at higher one. 5-hydroxytryptophan in reserpinised birds restored the temperature to normal level while with dopamine a significant rise was noticed particularly at room temperature 25 ± 1°C. The significant rise produced by dopamine in reserpinised birds seems to be due to the fact that the depletion of catecholamines by reserpine is a delayed process or may be due to tissues hypersensitivity mechanism.

4. Cyproheptadine (2 mg/kg i.p.), an anti-serotonin agent, produced fall in temperature returning to normal within 4-5 hour. This agent blocked only the initial gradual rise in body temperature caused by 5-HTP.

5. Yohimbine (2 mg/kg i.p.) did not show any significant effect on the body temperature of the fowl or the hyperthermic response to dopamine.

6. 5-hydroxytryptophan and dopamine did not show any marked gross observable effects in normal birds. In reserpine pretreated birds these two agents reduced the degree of sedation but dopamine was more potent. In nialamide pretreated birds 5-HTP and dopamine showed signs of stimulation whereas nialamide alone did not show any marked gross observable effects. Cyproheptadine showed sedative effects which may be attributed to its anti-5-HT and antihistaminic properties.

7. 5-hydroxytryptophan (0.5 mg/kg i.v.) in anaesthetised birds caused polyphasic response on blood pressure. Small doses of 5-HTP (5 to 50 mcg/Kg) produced only pressor response. The effect of 5-HT on blood pressure was variable. The effect of 5-HTP and 5-HT was blocked to a great extent by cyproheptadine (0.7 mg/kg).

8. Dopamine (0.05 mg/kg) and epinephrine (2.5 mcg/kg) showed pressor response which was markedly antagonised by yohimbine (0.5 mg/kg). Phentolamine (5 mg/kg) showed very little blocking action.

9. The results of the present investigations discussed in the light of work done on mammals show that :-

(a) 5-hydroxytryptamine, norepinephrine epinephrine and their precursor have definite hyperthermic neurotransmitter role in fowl.

(b) Changes in ambient temperature influence the hyperthermic response to biogenic amines quantitatively.

(c) The effect of 5-HT and its precursor on blood pressure of fowl is variable similar to in mammals.

(d) Little blockade of epinephrine pressure response by phentolamine indicates the presence of atypical α-adrenergic receptors in fowl.

CHAPTER VII

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