EFFECTS OF TEMPERATURE ON THE ACTION OF DRUGS[1,2]

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The use of hypothermia in medicine and surgery emphasizes the need for fundamental data on the action of drugs at different temperatures, but of primary importance are the effects of temperature on biochemical reactions in general. Studies of the influence of temperature on biological reactions are useful in the separation of physical and chemical processes, the latter being highly sensitive to temperature change, but they are not always easy to interpret. Calculation of a temperature coefficient is helpful in interpretation. One of the simplest and most commonly used, Q_{10}, varies with temperature except for the rare cases in which rate is an exponential function of temperature. Usually it decreases with increase in temperature and, at low temperatures, may greatly exceed the range of 2 to 3 which van't Hoff found for simple chemical reactions (41). If the logarithm of the rate of a reaction is plotted as a function of the reciprocal of the absolute temperature, a straight line is sometimes, but not always, obtained. A straight line is to be expected from the Arrhenius equation, in which the slope of the line, μ or E, has theoretical meaning (52). Where straight lines do not result (this in itself is informative), other mathematical treatments can be used. One of the most useful, the "b, α rule," has recently been given theoretical meaning by Bělehrádek (11) and has been shown to describe a wide variety of temperature-dependent processes such as protoplasmic viscosity, permeability, diffusion, and some enzyme reactions. According to Bělehrádek, the rate of biological processes is determined primarily by protoplasmic resistance opposing free movement of molecules. Application of this concept to drug-tissue interactions at different temperatures should certainly be made.

When this subject was last reviewed (31), several hypotheses were proposed to explain the differences in the actions of drugs at different temperatures. Since then the use of hypothermia and local cooling has become widespread, but there have been very few original investigations of fundamental biochemical processes at different temperatures. In contrast, there has been much interest in the practical applications of temperature differences and their effects on the action of drugs. This review does not include effects of hypothermia or cold exposure on secretion of adrenal cortical or medullary hormones. Also, the important topic of prevention of ventricular fibrillation

[1] The literature reviewed includes a few important publications which appeared between 1946 and 1955 and most of those published between 1955 and March, 1960.

[2] Abbreviations used in this chapter include: BAL (2,3-dimercaptopropanol).

during hypothermia is not included, since it has been fully discussed (3, 4, 23, 25, 45).

Environmental Temperature

Many authors still report differences in the toxicity of various drugs at different environmental temperatures. This type of experiment is not informative when the object of the research is an understanding of the fundamental action of a drug, and, sadly, some authors are still surprised to find that environmental temperature affects toxicity by changing body temperature. This has been recognized for many years and is entirely to be expected in small animals. The very careful work of Usinger (106) shows how body temperature of white mice can vary with environmental temperature. He found the body temperature to be 35.8°, 34.0°, 34.7°, and 37.2°C. at environmental temperatures of 20°, 25°, 30°, and 35°C., respectively. It would be preferable to study the effects of body temperature on toxicity, but it is certainly essential to control environmental temperature, and to measure body temperature, when studies of toxicity are made using small rodents. There is some practical value in experiments that show increased toxicity by increased absorption through the skin at high environmental temperatures (for instance, war gases), but the above precautions are necessary for correct interpretation of results.

Other physiological effects of environmental temperature are important in studies of toxicity. For instance, an environmental temperature of 38°C. is lethal to mice in three hours at a relative humidity of 20 per cent (2). The minimal rate of oxygen consumption in mice is at an environmental temperature of 30°C., but the rate increases both above and below this temperature. Blood flow through skin and subcutaneous tissue varies greatly with environmental temperature. Since small animals are so often used in studies of temperature and the action of drugs, these factors may influence results.

Shemano & Nickerson (95) found that there is a critical environmental temperature above which a given drug produces a rise in body temperature and below which it produces a fall. In rats this critical temperature is 30°C. for Hydergine (a mixture of the methanesulfonates of dihydroergocornine, dihydroergocristine, and dihydroergocryptine), ergotamine, *N, N*-diethyl-D-lysergamine (LSD-25), and 5-hydroxytryptamine; it is 36°C. for chlorpromazine, and about 20°C. for 2,4-dinitrophenol. In curarized dogs it is about 24°C. for pentylenetetrazol (96). The critical temperature depends upon the effects of the drugs on heat production and on heat loss.

The various types of relationships between the toxicity of a drug and environmental temperature may be graphically represented by the lines drawn in Figure 1,*A, B,* and *C*. The most common relationship is that given in Figure 1,*A,* in which minimum toxicity occurs at some temperature (Y) usually lying between room temperature and thermal neutrality (i.e., 17° to 30°C.). Toxicity increases at temperatures both below and above this point.

This relationship holds for chlorpromazine (9), α-naphthylthiourea (76), BAL (75), strychnine, atropine, digitalis glycosides, and many other drugs (57). Toxicity at temperatures X and Z may be equal, or either may exceed the other, depending upon the exact temperatures used. The relationship shown in Figure 1,*B*, i.e., continuously increasing toxicity with increasing temperature, has been found for dinitrophenol (33, 57), cortisone (91), ephedrine, methacholine, and other drugs (57). This relationship is less common than that shown in Figure 1,*A*. That in Figure 1,*C* is still less common but appears to obtain over a wide temperature range for procaine (57, 85), caffeine, pentylenetetrazol, and some other drugs (44, 57). It may, however, represent only the right-hand part of the U-shaped curve of Figure 1,*A*.

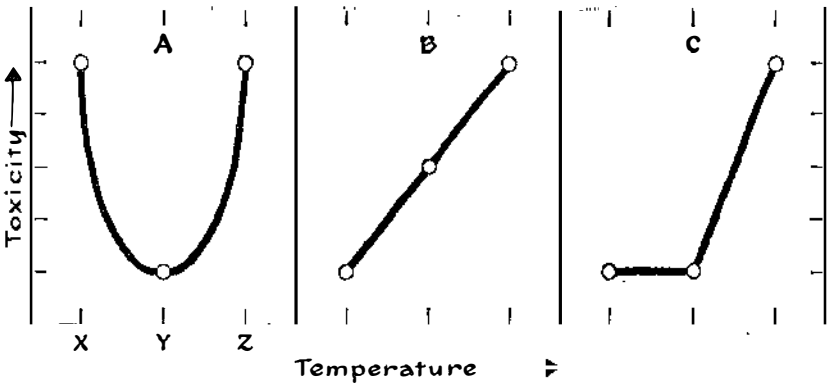

FIG. 1. Possible relationships between toxicity of drugs and environmental temperature.

In most published reports, the temperature range studied was not adequate to permit classification of the data into one of the relationships shown in Figure 1. It is well worth noting, however, that the relationships between toxicity and temperature which would be represented by the reciprocals of the lines drawn in Figure 1 have not been found.

Central nervous system depressants.—Synthetic analgetics [methadone, meperidine, and Hexalgon (1-piperidine-3,3-diphenyl-4-hexanone)] are about three times as toxic at an environmental temperature of 29° as at 18°C. when given subcutaneously to mice (42). This is not a result of difference in rate of absorption, since the same difference in toxicity was found at the two temperatures when methadone was administered intravenously. These authors (43) tried to relate toxicity to the concentration of the drug in the brain. Using an LD_{50} of methadone, it was found that the brain contains four times as much of the drug at an environmental temperature of 18° as at 29°C. Thus, there is a high brain concentration and a lower toxicity at the low temperature. But body temperature may fall to as low as 22°C. at an environmental temperature of 18°C., and, as the authors

suggest, the temperature of the brain may be lowered enough to protect the mice even though the concentration of the drug in the brain is high.

Komlós & Földes (59) reported that sleeping time of rats given hexobarbital was longer when either histamine or serotonin was used with it and that the increase in sleeping time was greater at an environmental temperature of 30° than at 20°C. Hexobarbital alone produces slightly longer sleeping time at 20° than at 30°C.

Berti & Cima (9, 10) administered chlorpromazine subcutaneously to mice. The relationship found conforms to that shown in Figure 1,*A;* at 28°C. the LD_{50} was 350 mg./kg., at 13°C. it was 12 mg./kg., and at 38°C. it was 30 mg./kg. At the higher temperature, death followed violent convulsions, whereas at the low temperature death followed prolonged central depression. Similar results were obtained by Srámková, Votava & Buda (98). Mice and rats pretreated with chlorpromazine cool much more rapidly than controls when placed in a cold environment (70, 95, 107), and rats also lose their ability to regulate body temperature in the presence of a heat load (14, 95). This "lability" of body temperature is much less evident in larger animals (19, 63). Thus, one might attribute the increased toxicity of chlorpromazine in mice at both high and low environmental temperatures to such sufficient interference with temperature regulation that death is partly attributable to hypothermia or hyperthermia. In mice, chlorpromazine produces a fall in body temperature at an environmental temperature of 22°C. (64). This effect is dependent upon dose; no fall occurs with doses under 1.5 mg./kg. Chlorpromazine also prolongs sleeping time after barbiturate injection at an environmental temperature of 22°C. It is well known that lowered body temperature prolongs sleep produced by barbiturates (32), but this result with chlorpromazine is not solely a result of decreased body temperature because it was found that at an environmental temperature of 36°C. where body temperature could not fall, the drug still prolonged sleeping time, probably by direct central depression. Reserpine (64), 5-hydroxytryptamine, and epinephrine (30) are similar to chlorpromazine in that they produce a fall in body temperature and prolong sleeping time with barbiturates or chloral hydrate.

Local anesthetics.— It has been known since 1937 that procaine is more toxic in mice at temperatures above 24°C. than at temperatures between 7° and 24°C. However, Pulewka & Berkan (85) showed once again that procaine and 3-dimethylamino-1,2-dimethylpropyl *p*-aminobenzoate (Tutocaine) are more toxic for mice at an environmental temperature of 37° than at 25°C. or below, whether the index of toxicity is death or convulsions. Although accelerated absorption occurs, this is compensated for by increased rate of excretion. Investigations were continued on rats because, in Istanbul, a thermometer small enough to measure the body temperature of mice was not available. Results on toxicity were similar to those obtained on mice (86). With procaine, rectal temperature of the rats fell at an environmental temperature of 22° and rose at an environmental temperature of 37°C.

The difference in body temperature was about 5°C. The animals at 37°C. became so hyperthermic (rectal temperatures were about 42.7°C.) that, we believe, death could have resulted from this alone, and it is unnecessary to propose, as the authors do, a further effect of procaine of producing anoxia. Inhibition of thermoregulation is clearly an effect of the drug.

Parasympathomimetic drugs.—The anticholinesterase, parathion (O,O-diethyl O-*p*-nitrophenyl thiophosphate), was administered intraperitoneally to mice kept at environmental temperatures of 35.6°, 22.8°, and 15.6°C. (7). It was about twice as toxic at 35.6° as at 22.8°C. and symptoms occurred much faster at 35.6°C. The results at 15.6°C. were complicated by delayed mortality.

Another anticholinesterase, sarin, has been administered intramuscularly to rhesus monkeys (26). It is more toxic at an environmental temperature of 38° than at 25°C. Body temperature fell at the lower temperature and rose at the higher temperature. In other experiments the monkeys were exposed to sarin vapor in a box that excluded their heads. Again the drug was more toxic at 38° than at 25°C., and there were small but definite differences in rectal and skin temperatures. This evidence suggests that, since muscle and skin blood flow are greater at 38°C., increased rate of absorption is responsible for the greater toxicity at high environmental temperatures.

Hormones.—Mice at environmental temperatures of 36°, 27°, and −6°C. were given 0.5 mg. cortisone acetate intramuscularly every 48 hours for eight days (91). Mortality was highest at 36° and lowest at −6°C. The control animals did not survive at −6°C., but those given cortisone lived. Cortisone administered with diphosphopyridine nucleotide is more toxic in mice at environmental temperatures of 37° and 7°C. than at room temperatures (40).

Miscellaneous.—The toxicities of H_2SO_4 mist (84) and CO (53) were reported to be greater at about 0°C. than at room temperature. But the toxicity of NO_2, which produces death from pulmonary edema, increases about 25 per cent with an 11°C. increase in environmental temperature (37). The greater toxicity was probably a result of larger respiratory volume at the higher temperature.

In mice given tetanus toxin, survival time decreases with increase in environmental temperature from 10° to 35°C. (49). Histamine is 25 times more toxic in mice at 37° than at room temperature (20).

At environmental temperatures of 0° and 37°C. the toxicity in mice of the venom of the Australian red back spider is 100 times as great as at room temperature (18° to 24°C.) (109). At the lower environmental temperature, death may result from hypothermia added to the effect of the venom, since body temperature fell 15°C. in three hours after injection.

Stahnke (99, 100) described the use of ligature and cryotherapy in the treatment of venomous bites and strings. Death, or extensive tissue destruction, can be prevented by immediate application of a very tight ligature

close to the site of injection of the venom and rapid cooling of the bitten hand or foot in crushed ice. Tissue temperature is thus reduced from 37°C. to about 4° to 7°C. while the body is kept warm. Cooling is continued while the ligature is released and absorption of the neurotoxic factor is slowed enough to prevent death. Bata & Vukobratovic (8) studied the effect of local cooling and hypothermia (18° to 20°C.) on the toxicity of viper venom in rats. Death was delayed, but not prevented, by either treatment. They state (in desperation?) that local cooling followed by amputation gives 100 per cent protection!

Body Temperature

There are several distinct, but interrelated, effects of body temperature on the action of drugs which, if not recognized, may make interpretation of data difficult and suggest contradictions where there are none. (*a*) The effect of body temperature on toxicity. Toxicity and duration or intensity of action may be affected quite differently by change in body temperature. For example, during hypothermia the toxicity of pentylenetetrazol is unchanged, while its duration of action is increased several hundred times. (*b*) The effect of temperature on duration or intensity of action. Changes in these aspects of the action of drugs during hyperthermia or hypothermia are frequently the result of the algebraic sum of the effect of temperature on absorption and on excretion or detoxification. (*c*) The effect of temperature on a process or function which reveals an action of a drug not apparent at normal body temperature. For instance, a concentration of acetylcholine, which has no effect on isolated rabbit atria at 37°C., re-establishes contraction abolished by cooling (74).

Central nervous system depressants.—The effects of central nervous system depressants added to those of hypothermia are complex but interesting. The well-known depression of the central nervous system caused by hypothermia is preceded by a hyper-responsiveness (58). The hyper-responsiveness is not caused by increased excitability, but by more extensive participation of interneurons in reflex action and by repetitive discharge of neurons following stimuli normally producing single responses. Certain depressants, such as ethyl alcohol (104) or benzene (97), when applied to peripheral nerves at low temperatures, produce repetitive firing, but neither cold nor the narcotic alone produces it. There is as yet no simple explanation for this, but an hypothesis based on membrane inductance has been proposed (97).

There have been very few investigations of the actions of central nervous system depressants at low temperatures, although they are used extensively for the induction of hypothermia. Chlorpromazine is one of the principal constituents of the *cocktails lytiques* used by the French for this purpose. When rats are given chlorpromazine before cooling, they cannot be cooled to lower rectal temperatures before cardiac arrest occurs

than without the drug (69). However, when rats are kept at a rectal temperature of 23°C., chlorpromazine prolongs survival 2.5 times (69). The toxicities of chlorpromazine in rabbits (6) and of pentobarbital in rats (94) increase during hypothermia.

Investigations of the detoxification of central nervous system depressants at low body temperatures have been made. Detoxification is, of course, an important determinant of the duration and intensity of action of these substances. The effect of temperature on detoxification is well illustrated by the studies of Rink *et al.* (88), who perfused isolated rabbit liver with blood containing morphine. Reducing the temperature from 37° to 24°C. increased biological half-time of disappearance of free morphine from the perfusate by 25 times.

The rate of oxidation of ethyl alcohol is reduced during hypothermia (50) as previous work had already shown (29, 31). Hypothermia, induced after administration of alcohol to rabbits, decreased both rate of absorption and rate of oxidation of the alcohol (50). Lowering the temperature of the chick embryo from 38° to 26°C. decreased the rate of oxygen consumption and of alcohol oxidation equally (28).

Central nervous system stimulants.—Bogdanovic (15) reported that in rats cooled to 16° to 18°C. by the Giaja method, the toxicities of cocaine and picrotoxin were increased, whereas that of strychnine was decreased [cf. also (35)]. He suggests that perhaps this difference is related to the different levels of the nervous system which these drugs stimulate. The opposite results were reported earlier on cats anesthetized with barbital (cf. 31). The toxicity of pentylenetetrazol, which appears to act at numerous levels, was not altered by hypothermia (15).

Owens (83) compared the effects of electrical stimulation and chemical convulsants on electroencephalogram (EEG) patterns at different body temperatures. Cats immobilized with succinylcholine were used. A given electrical stimulus (applied to the motor cortex) which produced seizure patterns at normal body temperature failed to do so at body temperatures below 26°C. But pentylenetetrazol or strychnine, injected intravenously in doses which produce minor changes in EEG at normal body temperature, produced very much greater response at low body temperatures. For example, a dose of pentylenetetrazol that lasted eight seconds at 37° lasted 18 to 20 minutes at 26°C.

Parasympathomimetic drugs.—There is much evidence now that the action of acetylcholine on the heart is greatly influenced by temperature. Turpaev (105), using electrically stimulated frog hearts at temperatures from 2° to 40°C., showed that acetylcholine, in a concentration of $1 \times 10^{-7} M$, had the maximum effect on amplitude at 18°C., and less effect above and below this temperature. At 3°C., even 1000 times this concentration had no effect. The heart of *Citellus* also did not respond to acetylcholine at 3°C., but the maximum sensitivity of this heart preparation was at 35° to 38°C.

Marshall & Vaughan Williams (74) studied the influence of acetylcholine on the excitation of isolated rabbit atria at low temperatures. This careful work showed that cooling to 14° to 20°C. abolished all activity except non-propagated pacemaker potentials. At these temperatures acetylcholine (10^{-6} to 10^{-8} g./ml.) produced propagated action potentials and contraction. This was potentiated by physostigmine and abolished by atropine (these drugs had no effect alone), and the doses of acetylcholine used had no effect at 30°C. The slowing of the dog heart produced by intracoronary acetylcholine (79) is greatly prolonged by lowering the body temperature to 24° to 27°C. König (60) found that the expected decrease in rate of the frog heart produced by acetylcholine could be prevented by cooling the sinus to 10°C., but when it was cooled to 5° or 1°C., acetylcholine increased the rate. This is rather surprising, unless differential cooling or block resulted in a ventricular rate independent of the cooled sinus venosus, but the author does not discuss this. Rindani & Merchant (87) found no slowing of the frog heart by acetylcholine below 20°C.

Sympathomimetic drugs.—It has been known for over 50 years that at low body temperatures the response to epinephrine is prolonged and that the effect which it produces on rate and amplitude of contraction of the heart is reduced. Although recent experiments have provided additional data, they have not greatly clarified the reasons for the observed differences in effects at low temperatures. Kruta (61) studied the effect of epinephrine on cooled perfused atria from various species of animals and found that the rate of guinea pig and rabbit atria increased more than that of rat atria. Hearts removed from rabbits cooled to 23°C. and then perfused at 23°C. were more sensitive to epinephrine than hearts removed from normal rabbits and perfused at 38°C. (78). A fixed dose (5 μg.) of epinephrine produced progressively less effect on heart rate and strength of contraction of perfused rabbit hearts as temperature was lowered from 40° to 20°C. (101). Booker (17) compared the effects of temperature on the action of epinephrine and norepinephrine on isolated perfused guinea pig heart. The threshold to both drugs was elevated 10 times by reducing the temperature from 37° to 25°C. The effect was also of longer duration at the low temperature. Low concentrations of cocaine that had a positive inotropic effect on the heart at 37°C. had only a negative inotropic effect at 25°C. (16).

The action of epinephrine is more complicated in cooled whole animals (cf. 21). Szekeres & Lénárd (101) found that in the cat a dose of 5 μg. produced less effect on heart rate, heart contraction, and blood pressure as the body temperature was reduced to 20°C., and that effects were greatly prolonged at the lower temperatures. At body temperatures of 15°C. this, or larger, doses had no effect on the heart rate of vagotomized anesthetized rats (22). These differences cannot be attributed to slowed circulation during hypothermia. Using a totally denervated rat heart and larger doses of epinephrine, Kayser (54) studied the heart rate with and without epine-

phrine at various temperatures. He found epinephrine less effective at lower temperatures. Calculated from the Arrhenius equation, μ was the same for the normal heart as for the denervated heart with epinephrine. The coefficient was smaller for the denervated heart without epinephrine.

Cotten & Brown (24) administered small doses of pressor amines intravenously to dogs at 36° and about 24°C., and measured the effects on the contractile force of the heart, systolic and diastolic pressures, and heart rate. The duration of action of all the drugs was usually about twice as long at the lower temperature. Effects of epinephrine, ephedrine, methamphetamine, phenylephrine, and methoxamine were either unchanged or moderately reduced during hypothermia. However, the effects of levarterenol on contractile force and blood pressure were much smaller during hypothermia than at normal body temperature.

Malméjac and co-workers have published many repetitious papers (three of which are cited here) describing effects of infusion of 1 to 2 μg./kg./min. of epinephrine in hypothermic animals. The epinephrine is reported to restore conduction in the heart (71), counteract ganglioplegia (72), and increase electrical activity of the cerebral cortex (73).

Neuromuscular and ganglionic blocking agents.—The excellent work of Holmes, Jenden & Taylor (46), using strips of rat diaphragm stimulated directly and via the motor nerve, describes the action of tubocurarine at different temperatures. Seperate equilibrium and kinetic experiments were performed to distinguish between factors affecting the activity of the drug and the rate of action. In equilibrium experiments it was shown that a reduction of temperature from 40° to 26°C. reduced neuromuscular blocking action. Further decrease in temperature potentiated blocking action. Then, using a dose large enough to block neuromuscular transmission at all temperatures, they found that the speed of paralysis is determined by rate of diffusion of the tubocurarine to the site of action. When the logarithm of the velocity is plotted as a function of the reciprocal of the temperature, a straight line results, and μ is 5100 (Q_{10} about 1.3). Removal of the drug from the site of action is also determined by diffusion. However, according to Segre (92) the action of tubocurarine on the diaphragm does not follow the Arrhenius equation.

Using cats anesthetized with chloralose and pentobarbital and cooled, Bigland *et al.* (13) studied the action of tubocurarine on the contraction of the tibialis muscle after stimulation of the sciatic nerve. Various types of experiments were used such as keeping one leg warm while the other was cooled, keeping the body warm while the leg was cooled, etc. They found, as did Holmes, Jenden & Taylor (46), that tubocurarine is a less effective blocking agent at 25° to 30° than at 38°C. Also, the duration of block was not affected by decrease in temperature. In further experiments (13), other blocking agents, succinylcholine and decamethonium, which act by depolarizing the motor end plate, were studied. It was found that with a given dose

of either drug, the duration of action was much longer at low temperatures (the duration was four times as long at 31° as at 36°C.), and cooling increased the magnitude of the blockade. Thus, decrease in temperature has an opposite action on blockade by these two agents and blockade by tubocurarine. The effect of temperature on blockade by succinylcholine and decamethonium is about the same; yet the former is rapidly hydrolyzed by plasma pseudo-cholinesterase whereas the latter is excreted. Thus, the effect of cooling in increasing block is probably not the result of slowed enzyme action. Both drugs depolarize motor end plates, and recovery from depolarization is greatly slowed by decrease in temperature (27). This is probably the explanation of the more effective block at low temperatures. It might be presumed that lowering the temperature should make acetylcholine more effective (since succinylcholine acts like acetylcholine), thus reducing the effectiveness of drugs that compete with acetylcholine. Since the action of tubocurarine depends on competition with acetylcholine, it would be less effective as a blocking agent at low temperatures; this was the experimental result. Much of this work on blocking agents was repeated on human subjects with the same results (18).

Histamine and antihistaminics.—The effect of temperature on the release of histamine seems to depend upon the nature of the histamine liberator. Monger & Schild (77) found that the release of histamine from guinea pig lung by egg albumen *in vitro* was maximal at 40° and absent at 20°C. In hypothermic rats at 14° to 16°C., less histamine is released by intraperitoneal dextran than in controls (108). Release of histamine by intradermal dextran was also decreased by cooling. In the excellent work of Halpern, Neveu & Brannellec (38), blood histamine was measured in rats cooled by the Giaja method to a body temperature of 15°C. After administration of basic amines [*p*-methoxy-N-methyl-phenethylamine (48/80) and 1935L] blood histamine was higher in hypothermic rats than in controls. This was probably a result of decreased rate of destruction of histamine. But the liberation of histamine by dextran was completely blocked by hypothermia. This is good evidence that, at least in hypothermia, there is a dual mechanism of liberation of histamine which is influenced by the physicochemical nature of the histamine-liberating substance.

The effect of temperature on the antagonism between histamine and pyrilamine and histamine and diphenhydramine was studied in guinea pig ileum (93). Gillespie showed that hypothermia decreases the volume and acidity of gastric secretion induced by histamine in the cat (36). However, when gastric acid secretion was recorded continuously in the rat, moderate cooling increased the response to histamine and moderate heating decreased it (34).

Cardiac glycosides and aglycones.—Digitalis and related compounds are less toxic and less effective in homeotherms when body temperature is below normal. Recent evidence is in complete agreement with much older data

on frogs, etc. (cf. 31). The dose of digilanid necessary to produce cardiac arrest in cats is twice as great at 25° as at 37°C. (89). In hypothermic dogs, more ouabain (5) and more deslanoside (80) were required to produce typical digitalis effects than in normothermic animals. Ouabain was less effective in increasing the contractile force of the heart in hypothermic dogs than in normothermic dogs (24).

Saunders & Sanyal (90) used electrically stimulated strips from guinea pig ventricle to study the action of ouabain at temperatures from 17° to 37°C. Change in temperature had a negligible effect on the rate of onset of action of ouabain, but the positive inotropic effect increased with increasing temperature. The relatively small effect at low temperatures may be caused by low intracellular potassium at low temperatures.

Metabolic inhibitors and stimulants.—In dogs cooled to 20°C., the chemoreceptors in the carotid body still respond to cyanide (81). More cyanide is required to produce death of hypothermic (28°C.) dogs than of controls (51).

During hypothermia the behavior of a young mammal and a hibernator differs from that of an adult homeotherm, the two former continuing to respire at lower body temperatures. It is well known that glycolysis is much more important during the first few days after birth than in the adult, and one may ask if the resistance to cold of the newborn homeotherm and the hibernator is caused by a special property of the nervous tissue of the center or of the myocardium. Kayser attempted to answer this by determining the effect of metabolic inhibitors and a stimulant on QO_2 of these tissues at different temperatures. Malonate depressed the QO_2 of hamster brain slices less than the QO_2 of rat brain slices at 38°, 30°, 23°, and 16°C. (56). Depression of rat brain QO_2 was similar at all temperatures, but there was less inhibition of hamster brain QO_2 at the lower temperatures. Dinitrophenol produced the same inhibition at all temperatures [this result differs from that of Fuhrman & Field (cf. 31) and Locker (see below)]. Iodoacetate depressed the QO_2 of hamster heart less than that of rat heart at temperatures from 16° to 38°C. (55).

Locker tested the effect of various concentrations of 4,6-dinitro-*o*-cresol on the QO_2 of tissues in Ringer-bicarbonate (without substrate) at different temperatures from 17.5° to 42.5°C. Two types of response to 4,6-dinitro-*o*-cresol were found. (*a*) In frog and toad liver (65, 68) maximum stimulation of QO_2 occurred at about 32.5°C. or higher, and stimulation decreased (or became inhibition) with decrease in temperature. (*b*) In the liver of the mouse, rat, and guinea pig and skin of frogs (66, 67), maximum stimulation occurred at or below 22.5°C. and decreased with increase in temperature. Locker interprets his data according to the theories of enzyme inhibition developed by Johnson & Eyring (52), based on the concept that enzymes exist in equilibrium between a catalytically active and inactive form.

Miscellaneous drugs.—Hasegawa & Matsuda (39) and Takahashi &

Matsuda (102) determined the time required for various drugs (digitalis, strychnine, acetylcholine, etc.) to produce characteristic effects on toad and fish hearts and perfused toad limbs at various temperatures. Values for Q_{10} were usually between 1.5 and 2.5. They state that these coefficients reflect differences in adsorption of the drugs and come to the astonishing conclusion that this explains all differences in actions of drugs, and that it is unnecessary to assume any chemical changes in them or any changes in cell metabolism.

The toxicity of dipicrylamine in fish is the same at 20° and 3°C., but the time required to produce the first signs of poisoning after injection is longer at the lower temperature (103). When rat uterus was cooled *in vitro* to 23°C. with oxytocin added to the fluid around it, the phasic contractions associated with action potentials were suppressed (62). Cooling the isolated guinea pig ileum to about 20°C. abolishes the emptying phase of the peristaltic reflex; introduction of small amounts of 5-hydroxytryptamine into the lumen restored peristalsis (12).

The hyperglycemia produced in rabbits by injection of pentobarbital at a body temperature of 38° fails to occur when this drug is injected at 27°C. (1). The same authors also confirm older observations that insulin hypoglycemia is greatly delayed or prevented by cooling.

The antidiuretic action of exogenous posterior pituitary hormone is reported to be absent in hypothermic rats (47). This hormone increases water uptake through the skin of frogs, and the effect is abolished by cooling the frogs to 1°C. (48).

Olsson, William-Olsson & Lagergren (82) found that the elimination of heparin from plasma is exponential in both normothermic and hypothermic dogs. The average time for 50 per cent decrease in plasma heparin was 63 minutes at 36° and 128 minutes at 29°C.

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