THE EFFECT OF TEMPERATURE ON THE ACTION OF DRUGS[1]

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INTRODUCTION

The effect of temperature on the action of drugs in animals and man has interested physiologists and pharmacologists for a long time. Several review articles have appeared in the last 25 years. In some, theeffects of body temperature (22, 38, 92) were differentiated from those of environmental temperature (40, 90) on drug action. The effects of climate were considered by K. I. Furman (41) and Weihe (111). F. A. Fuhrman (39) and K. I. Furman (42) reported on the effects of heat, and Johnson (66) on the effects of cold. A different approach to the problem dealing exclusively with the sensitivity of laboratory animals is presented in the reviews by Laroche (75) and Ellis (34). All these reviews deal chiefly with experiments on animals which demonstrated striking effects of heat and cold on drug toxicity.

Many proceedings of symposia and review articles have been published since 1960 on the mechanism of temperature regulation and the physiological effects of heat and cold (13, 33, 51, 52, 55, 76, 94) and on temperature regulation and drugs (77, 83, 108, 109). In the same period, publications dealing with the specific problems of alteration of drug action by temperature or climate in man are rare (39, 41).

Most investigations on the modification of drug action were done with common homeothermic laboratory animals. They demonstrate either a variation of results in drug testing due to an improperly controlled thermal environment, or a change of sensitivity of the animal to drugs under controlled conditions of heat and cold. New problems have arisen from toxic effects of environment pollution in various climatic zones. Here, too, little has been published as yet. This paper will deal only with homeothermic species not subjected to induced hypo- or hyperthermia.

THERMOREGULATION

Normally, homeothermic species show a very small variation of core temperature within 24 hours. On exposure to extreme heat ($>T_a$ 33°C) and cold ($<T_a$ 15°C) mice and rats maintain their body temperatures by means of powerful

[1] Parts of this review were presented at the Symposium on the Pharmacology of Thermoregulation, San Francisco, 29–31 July 1972, and are published under the title "The effect of temperature on the action of drugs" in "The Pharmacology of thermoregulation" edited by P. Lomax and E. Schonbaum, Karger, Basel, 1973.

homeostatic mechanisms. In mice, Chen et al (17) measured at an ambient temperature (T_a) of 20°C a rectal temperature (T_{re}) of 34.7°C and at T_a 40°C a T_{re} of 38.5°C. Doss & Ohnesorge (30) found in mice after 150 min at T_a 35°C a T_{re} 38.4°C and at T_a 30°C a T_{re} 36.8°C. At T_a 15°C the T_{re} was 36.6°C. Usinger (106) working with 30°C adapted resting mice, recorded a decrease of T_{re} from 35.6° to 35.1°C after a change to T_a 20°C. In rats, Maickel (79) measured after a 4-hr exposure at T_a 4°C a decline of 1.3°C T_{re} (37.8–36.5°C). Differences of T_{re} up to 3°–4°C in mice and to some extent in rats are large and occur only with exposure to extreme ambient temperatures below 15° and above 33°C. At normal T_a the amplitude of T_b is up to 1.5°C for the rat (11) and also for man (2, 57, 82). Preoptic temperature in rats and cats eating food at ambient temperature of 20°C showed a variation of 1.1°C and after a chilled meal in cats 1.4°C (1, 46).

Core temperature is kept constant by alterations in the peripheral insulation affecting amount and speed of heat loss, or metabolically by increasing or reducing metabolic rate. The mechanisms of insulative and metabolic functions and their adaptation during acute and long-term exposure to extreme thermal conditions have been thoroughly investigated in comparative studies in animals and man (7, 50, 52, 54, 55).

There is an important difference between the common laboratory animals (such as the mouse, rat, guinea pig, rabbit) and man in their mode of regulation of body temperature on exposure to cold and heat due to the experimentally enforced restriction of behavioral temperature regulation in the animals. Laboratory animals in confinement adapt to heat and cold metabolically while man responds through control of heat loss with insulative adaptation.

Metabolic adaptation to cold can occur in two ways, either by shivering or nonshivering thermogenesis. Shivering is observed in acutely exposed nonacclimatized animals, and as acclimatization takes place with chronic cold exposure nonshivering thermogenesis develops. The mechanisms of the two forms of thermogenesis have been described in detail by Smith (100) and Smith & Hoijer (101). The thermoneutral zone of resting laboratory animals and man is very small. If opportunities for behavioral control of temperature regulation are provided, the thermoneutral zone widens and the increase of heat production with decreasing T_a becomes less.

This has been emphasized by recent comparative studies on behavioral temperature regulation (13, 51). Behavioral temperature regulation is the active control of heat production and loss, utilizing food and water uptake, changes of posture and activity, nest building with bedding material, huddling, aggregation or disaggregation, and clothing for man. Behavioral temperature regulation is a way of controlling insulation beyond the skin.

General Considerations

The living body is a mass with continuous heat production, heat flow from the core to the surfaces, and heat loss to the environment. The flow depends on the gradient between core temperature T_b and T_a. If the thermal gradient T_b–T_a is large, skin and peripheral tissue temperature will be low. Therefore, Aschoff &

Wever (3) differentiated between the core and the shell of the body. At high T_a much heat is stored in the body and T_s is nearly as high as T_b. Accordingly the core extends to the body surface, whereas at low T_a it shrinks and is finally limited to the central parts. This shift in the width of the heat buffer in the tissues is more significant for the limbs where the surface/mass ratio is large than for the trunk of the body where it is small. The homeostatic drive is so strong that core temperature will not change as long as the heat regulation mechanisms are not damaged or exhausted.

The metabolic rate of the tissues follows the Q_{10} rule. The application of this rule to the absorption and metabolism of drugs at different tissue temperatures has been discussed by Fuhrman (39). In a homeothermic organism changes of the Q_{10} values will occur more frequently in the unprotected tissues of the body shell, and less in the core where the temperature variation is small.

The absorption and action of a drug should therefore be affected by ambient temperature if it is administered and/or acts at the periphery as with epicutaneous, subcutaneous, and intramuscular administration. The temperature of the peripheral tissues is of little or no significance when drugs that do not act peripherally are administered either intravenously or orally.

THE PHYSICAL ENVIRONMENT

Temperature is the parameter of the physical environment most frequently used in defining thermal conditions. Humidity is usually treated separately, though it contributes significantly to the thermal environment as latent heat. Reports on the effects of high or low humidity may be misleading without reference to temperature and heat loss by convection and radiation.

The reason for limiting the thermal parameters to temperature in investigations seems to be either the tendency to simplify correlations or the lack of equipment to control and record anything but temperature (96). Often not even temperature is properly recorded (87). It should always be borne in mind that temperature is only one of a number of factors that determine the thermal conditions in the environment.

The thermal conditions of the biosphere are described in meteorological terms as weather and climate. Weather corresponds to short-term exposures lasting from hours to a few days. Acclimatization of the body will not take place during such a short time. Climate corresponds to long-term exposure with acclimatization of the body. Man is ingenious in providing a thermoneutral climate around his body or in his enclosures and avoids direct exposure to the weather and climatic extremes. Patients confined to bed are particularly well protected.

OBSERVATIONS IN LABORATORY ANIMALS

Acute exposure.—The majority of studies of drug action in animals at various ambient temperatures have been done with mice and rats. A random selection of 60 publications during the last five years showed 16 papers on the mouse, 32 on the rat, 8 on the guinea pig, and 4 on cats and dogs. A list of the toxic

doses of drugs in animals at various temperatures, mentions only mice and rats (39). Most investigations utilized nonacclimatized animals acutely exposed to heat or cold. The exposure time before drug administration ranged from 30 min (58) to 8 hours (9). As these small animals must adjust their physiological functions rapidly, drugs were administered during a phase of great physiological change.

Unfortunately in the majority of studies the description of experimental procedures is incomplete, as there is no record of the conditions under which the animals were exposed: e.g., singly or in groups, size of groups, and type of cage (wire mesh or boxes with bedding). The details are of great importance for the understanding and interpretation of drug toxicity.

This was clearly demonstrated in studies designed to determine optimal group size and conditions for drug testing. Chance (15, 16) in determining the LD_{50} of amphetamine in cages of similar size at 27°C found values of 117.3, 89.5, and 90.0 mg/kg for single mice and 14.0, 7.0, and 13.7 mg/kg for groups of 10 mice. This represents a 9–10 fold difference. At 15.5°C T_a the LD_{50} was 197.0 for single mice and 141.4 mg/kg for 10 mice per cage. Single and grouped mice were very active at T_a 27°C and quiet at 1.5°C. The sensitivity scale from high to low toxicity was as follows: warm grouped mice, warm single mice, cold grouped mice, cold single mice.

The difference of amphetamine toxicity in single and grouped mice was confirmed by others (4, 18, 110). Askew (4) exposed his mice at T_a 26° and 21°C. In grouped mice, rectal temperature (T_{re}) increased 1.4–4.0°C at T_a 26°C and 0.5–3.0°C at T_a 21°C. In single mice at T_a 26°C, T_{re} increased 1–2°C or fell. Doss et al (31) also observed hypothermia in single mice at T_a 20°C and 15°C after nontoxic doses of amphetamine.

Considering that amphetamine increases the metabolic rate, the sensitivity scale developed by Chance (15, 16) and Askew (4) could mean that the more body cooling was facilitated the lower the toxicity of amphetamine (20). An additional release of adrenaline due to crowding in some of the experiments cannot be excluded. Dolfini et al (29) measuring T_b of grouped mice at 4° and 30°C after 10, 30, and 45 mg/kg *d,l*-amphetamine intraperitoneally found a decrease of T_b after 120 min, which was almost 5°C after 10 mg, and 12°C after 45 mg/kg. Therefore at low T_a amphetamine even facilitates cooling by interfering with behavioral temperature regulation. Hardinge & Peterson (49) observed an increase of toxicity with increase of ambient temperature for single mice over a T_a range of 20–32°C. Restriction of movement at 32°C to reduce heat production from overactivity significantly protected both isolated and grouped mice. Aggregation of 3 or 9 mice per cage increased toxicity 4 times at T_a 26°C. When the mice were cooled by a rapidly moving air stream this aggregation effect was eliminated. Single mice in close proximity, with their movement much restricted, in 20 cm^2 compartments at T_a 26°C tolerated as much drug as isolated mice. On the basis of their studies Hardinge & Peterson (49) concluded that the differences in amphetamine toxicity were due to the differences in heat production and heat loss in single and grouped mice.

Grouped mice will always aggregate to minimize heat loss in the cold and separate to maximize heat loss in the heat. Work with hairless and white mice singly and in groups of 2 and 6 in wire mesh cages, has shown that the energy requirement, measured by food intake, was greatly reduced for grouped animals (113). While single animals increased their food intake linearly with decreasing T_a below the lower critical temperature of about 28°C, grouped white mice only began to increase their food intake at T_a as low as 20°C and the rate of increase of food intake at lower T_a's was small. This conservation of energy due to huddling could be increased when bedding material was provided instead of open wire cages.

Müller & Vernikos-Danellis (88) determined the LD_{50} of *d,l*-amphetamine intraperitoneally in grouped mice (10 mice per cage) 15°, 22°, and 30°C after 1-hour and 3-day preinjection exposures. As might be expected, the 3-day acclimatization period did not change the toxicity because behavioral temperature regulation operates in this moderate temperature range that is of little stress (112).

These examples are quoted to emphasize the need for a proper experimental design for comparative studies intra- and interspecies. The aim should be to eliminate or reduce or to provide opportunities for behavioral temperature regulation so that the animals are fully exposed to or have a chance to protect themselves against the actual thermal conditions. The introduction of a rigid standdardization scheme to minimize or maximize behavioral temperature regulation is recommended (26, 79).

It has been pointed out that the different response of animals to drugs at various T_a's is due to the change of body temperature (34, 38, 92). This might be inferred from the circadian change of sensitivity to drugs (91). T_b varies with exercise, food consumption, and rest. The contention that the resetting of T_b is the principal reason for the change of sensitivity in the heat and the cold is not convincing and unproven. In many experiments the exposure time before administration of the drugs was not long enough and the thermal conditions not extreme enough to produce a larger change in the amplitude of the 24-hr T_b cycle.

These observations apply to normal, unrestricted animals. Even slight restriction can affect drug responses, particularly when animals are exposed to extreme T_a's higher than the mean T_b, as in experiments by Shemano & Nickerson (98). They exposed rats in wire mesh tubes with recording of T_{re} for 2 hours before and 3 hours after drug administration. In controls at T_a 39°C, T_{re} was 40.6°C, which is 3.5°C above normal (37.0°C). After chlorpromazine, thermoneutrality was at T_a 36°C, which is the highest value reported for any drug, and about 6°C higher than the values found by other workers (see 39,90). Under the same experimental conditions the thermoneutrality was found to lie at T_a 30°C for hydergine, ergotamine, LSD-25, and serotonin.

An analysis of the patterns of toxicity of drugs in mice and rats by Fuhrman & Fuhrman (40) resulted in 3 types of toxicity versus T_a curves: (*a*) the V- or U-shaped type with minimum toxicity around thermal neutrality and increasing toxicity at lower and higher T_a's; (*b*) a linear type with increasing toxicity with increasing T_a; and (*c*) an angled line type with constant values of toxicity at

low T_a up to the thermoneutral zone and increasing toxicity at T_a above the upper critical temperature.

The most impressive type of response is certainly type (*a*) with increasing drug toxicity at temperatures below and above the thermoneutral zone. The curve for metabolic rate as a function of T_a is similar (50, 54), so that toxicity increase parallels metabolic rate. The U-shaped response might be due to widening of the thermoneutral zone by behavioral temperature regulation. This hypothesis should be confirmed, but according to available evidence toxicity of type (*a*) drugs is determined by metabolic rate rather than by resetting of the body temperature. Interestingly enough, this group includes drugs that produce hypothermia, such as chlorpromazine (9) and reserpine (25).

The type (*a*) toxicity curve is characteristic of many centrally acting drugs affecting the thermoregulatory center. These drugs include the hypnotics and neuroleptic drugs such as phenothiazines, monoamine oxidase inhibitors, rauwolfia alkaloids (reserpine), morphine, cholinergic blocking agents, salicylates and other antipyretic drugs, digitalis glycosides and others (see 39, 40).

The other important type of response is the increase of drug toxicity with increasing T_a. Well-known examples are sympathomimetic drugs such as amphetamine and methamphetamine (4, 31, 49), epinephrine and norepinephrine (93), procaine (99), cortisone (96), analeptics such as picotoxin (17) and antihistamines such as diphenhydramine (72).

The final type of drug response is debatable, as pointed out by Fuhrman & Fuhrman (40) when they first described it. Possibly drugs of this group will prove to be type *a* or *b* if adequate conditions for exposure are provided that make impossible an extension of the thermoneutral zone into the range of low T_a by behavioral temperature regulation. Procaine, for example, was originally included by Fuhrman & Fuhrman (40) in the type *c* group but is now considered a member of the type *b* group.

In general, acute exposure of small homeothermic animals to heat and cold is followed by a change of metabolic rate with decreased or increased heat production. Drugs that affect heat production centrally or peripherally so that the animals become poikilothermic and are at the mercy of the environmental thermal conditions are most likely to show the lowest toxicity at physiological thermoneutral conditions. Drugs that stimulate heat production, such as sympathomimetic drugs, may show a linear correlation of increasing toxicity with increasing ambient temperature.

These relationships are interesting and important in drug screening and the investigation of mechanisms of drug action or the function of temperature regulation. A knowledge of them is fundamental in the choice of the appropriate experimental conditions for the animal model. To prove the effect of a drug on metabolism or on functions controlling heat loss, animals must be studied within an ambient temperature range in which an increase of the metabolic rate can be ensured (105). The interference with homeothermia by blockade of adrenergic functions or stimulation of cholinergic functions can only be demonstrated in cold-exposed rats (79). For such studies the animal kept at thermal neutrality is an unsuitable model.

Chronic exposure.—Only a few experiments have been carried out on the administration of drugs to chronically heat- or cold-exposed animals. The cold-acclimatized rat and mouse differ in many ways from animals living at room temperature (53, 54). The most important change is the increase in metabolic rate by nonshivering thermogenesis. There is an increased sensitivity to the calorigenic action of norepinephrine and its toxicity seems to be higher. In 2°C acclimatized rats chlorpromazine produced only a transitory fall in T_b and the toxicity of reserpine was lower than in normal rats (67). When rats were given chlorpromazine (10, 20, and 40 mg/kg s.c.) after 15 weeks acclimatization at 2°C they showed an increased urinary excretion of noradrenaline and to a lesser extent adrenaline as a result of the temporary hypothermia (65). The toxicity of isoprenaline in rats exposed for 7 days at 4°C increased 100 times in males and 10,000 times in females compared with normal rats (6). In comparative studies on rats exposed to 0°C either for 30 minutes or 8 days, Jonec & Murgas (69) found a significant difference in the effectiveness of amphetamine, physostigmine, neostigmine, and dexamethasone. The observations were based on the response of the adrenals and showed an increased effectiveness in cold-acclimatized animals.

Hässler et al (56) reported that the duration of action of hexobarbital in rats raised at 0° to 4° is prolonged if tested at 27°C at the age of 60 and 120 days compared with controls.

Long-term studies in the effect of weather-dependent changes of temperature and humidity were carried out by Tolcsvai-Nagy et al (104) on the behavior of cats and by Stille et al (103) on the behavior of mice, without administration of drugs. Temperature and humidity change affected the voluntary activity without apparent influence on the metabolic rate.

In former times researchers could reach misleading conclusions due to unawareness of cold acclimatization in their animals. Glover et al (44) reported that the noradrenaline sensitivity of isolated perfused rabbit ear arteries increased by about 40% with cooling of the arteries from 37° to 25°C. McClelland et al (80) were able to reproduce this effect only with animals from an old animal house but not after moving the colony into a new building. They compared arteries of rabbits after 3–6 weeks at 5°C and 21°C and found that arteries from cold acclimatized animals had an increased sensitivity and arteries from normal temperature animals had a decreased sensitivity to noradrenaline at 25°C.

Observations in Man

After the exciting reports of changes of drug toxicity in small animals under laboratory conditions, the responses of man to drugs in the heat or cold are disappointing. The statement by Fuhrman in 1963 that "very little detailed information exists concerning the modification by heat of the action of drugs in man" can be extended to modification by cold as well, and holds true for both extremes of ambient temperature to this day.

If on the one hand information is accumulating steadily from animal experiments and on the other hand there is no corresponding information for man, this could be due to a difference between the two systems, animal model and

man. As already pointed out homeothermia in man is better controlled than in small laboratory animals and man's metabolic rate changes little either in the cold or in the heat (12, 102).

Man maintains as constant a microclimate around his body as possible. It is said that in the arctic man's microclimate underneath his clothing is similar to that of his fellow man in the tropics. In a rare experiment healthy human beings were persuaded to expose themselves for 40 hours weekly for 5 weeks in a semi-nude state at T_a 5°C to achieve a state of cold acclimatization at which the calorigenic action of norepinephrine was found more effective than in persons not cold-acclimatized (71). The same was demonstrated in rats (27).

The effective protection against heat and cold loads is achieved by man through very effective physical heat regulation (sweating, vasodilation, vasoconstriction, etc.), in combination with his unique means for behavioral temperature regulation. Climate-induced modifications of drug effects can only be expected where either the central heat regulation control and/or behavioral temperature regulation is disturbed.

However, on the basis of the observations in laboratory animals similar effects must be anticipated in man. Fundamental differences will only be seen where the physiological properties of man are different from those of animals. This applies to the atropinic drugs, which inhibit sweating in man, a property not seen in small animals. Because of this, atropine has become the pet drug of climate-induced drug modification (39).

Jahnke (64) reported that in the hot dry climate of Baghdad small doses of atropine used in an ophthalmalogical practice were fatal, as sweating was inhibited and rectal temperature rose. Wetting of the skin to simulate sweating resulted in immediate relief of complaints. Jahnke went on to say that the action of many other drugs "might perhaps be changed" in the heat though he did not give any examples. At that time the embarrassing complication of heat stress from intramuscular injection of 2 mg atropine sulfate to nonacclimatized and partially acclimatized healthy individuals in hot dry (43°C, 36% RH) and warm moist (32°C, 81% RH) climate was already known (23). Even with 30 days acclimatization to heat for several hours daily, the inhibition of sweating after atropine sulfate did not change (21). Safer (95) noted that the mental and motor impairments induced by a low deliriant dose of scopolamine hydrobromide (10 mg/kg) were significantly increased at ambient temperatures of 35° and 40.5°C. This would be in agreement with observations in mice by Chen et al (17) who found increased toxicity above 30°C ambient temperature.

A search for further information from hot and cold countries was most discouraging. F. G. Sulman (Department of Applied Pharmacology, Jerusalem, personal communication) has not observed any change of drug action from heat in Israel. H. Friebel (World Health Organization, Geneva, personal communication) has received no notification either from tropical or from subarctic countries on modification of drug action by heat or cold.

One example of climate-induced drug effects by inhibiting of the sweating mechanism in the heat has already been mentioned. Other examples can be

found if the blocking of behavioral temperature regulation is considered, as with sedation and anesthesia. Such treatments take place under widely varying ambient thermal conditions.

In former times hospital operating rooms showed striking seasonal changes of thermal conditions. Nowadays most operating rooms and intensive care units are air conditioned but most hospital wards are not. This is particularly important in psychiatric hospitals where large amounts of neuroleptic drugs are administered and little nursing care is available.

Goldberg & Roe (45) mention that hyperthermia during anesthesia was attributed to high T_a and RH in operating rooms as early as 1916. They recorded T_{re} in adult patients undergoing various operations. The average T_a of the operating room was 20–23° and 55–55% RH. Patients were draped in a "standard fashion". Premedication consisted of atropine or scopolamine and meperidine. For inhalation anesthesia, nitrous oxide and cyclopropane were used. Out of 101 patients, 78 had a fall of T_{re} of 0.43°C with closed peritoneal cavity and 0.7°C when the peritoneal cavity was opened. The longer the operation lasted, the greater was the change of temperature. The observation was age-dependent as it was more striking in elderly patients. The heat deficit in patients over 60 years was 12.9 kcal/(m^2.hr) or twice as high as that of patients between 20 and 39 years (5.6 kcal/(m^2.hr). Morris & Wilkey (86) and Morris (84, 85) postulate a "critical ambient temperature" in operating rooms with standard draping of the patient lying between 21° and 24°C, at which normothermia will be maintained with usual premedication and inhalation anesthesia (halothane, methoxyflurane) or a narcotic.

Clark et al (19) measured the air temperature under the drapes at T_a 26.5°–32°C, which was 4.5–5.5° higher than the T_a and approaching body temperature. With the elimination of behavioral temperature regulation under anesthesia, hyperthermia can easily develop from heat accumulation around the body due to too much draping as well as hypothermia due to too little insulation against heat loss.

Some observations have been published on the effect of temperature on the action of centrally acting drugs, mainly phenothiazines. Hollister et al (60), reporting on the treatment of about 600 schizophrenic patients in Palo Alto, found changes of oral temperature uncommon. If changes occurred, T_{or} was decreased. A description of the environment was not given. Ayd (5) stated that many patients taking 300 mg chlorpromazine daily report hypersensitivity to freezing temperatures in cold weather and hypersensitivity to the heat load in hot humid weather. They emphasized that in the early stages of treatment with large doses (500 mg or more daily) the patients lose behavioral temperature regulation due to lethargy and impairment of piloerection and vasoconstriction. Hypothyroidism predisposes to hypothermia. Jones & Meade (70) reported on two elderly myxedematous patients who were treated with chlorpromazine. On admission to the hospital their T_{re}'s were 32.0° and 29.8°C. When room temperature and thyroxine treatment were raised the T_{re}'s returned to almost normal values within a few days. In the hot summer climate of New York City Shapiro

(97) described a case of severe hyperthermia in a 56-year-old man, who had swallowed large doses of trifluoperazine, was fully dressed and had walked around in the City at 33°C. Ext (35) reported that in a New York City hospital during a heat spell several patients who were given mepazine developed heat stroke with hyperthermia, which was not seen in untreated cases at that time. During a hot spell with temperatures as high as 40.5°C in Waco, Texas, 25 patients receiving mepazine developed heat stroke. In each case the role of mepazine in rendering the patient susceptible to heat stroke was recognized. This was not seen with other phenothiazine derivatives (37). Another example of mepazine-induced hyperthermia during a heat wave in New York City (T_a 34°C, 60–80% RH) was reported by Mahrer et al (78). In this patient perspiration had entirely ceased. He recovered after his body was covered with wet bed sheets on which a fan was directed.

During a humid heat wave in the midwestern states in July 1969 Zelman & Guillan (114) have seen 3 cases of fatal hyperthermia following large doses of chlorpromazine (~500 mg) in Topeka, Kansas. They had additional treatment with anticholinergic drugs, suppressing their sweating mechanism, which made them even more susceptible to heat stroke. Two cases of hypothermia were observed during treatment of carcinoid with high doses of parachlorophenylalanine alone and in combination with perphenazine. Ambient thermal conditions were not considered (107). Exton-Smith (36) warned physicians that the dosage of chlorpromazine, particularly in old patients, should be reduced or discontinued in periods of very cold weather and shortage of heating material. The increased heat loss in cold water has caused severe hypothermia in psychiatric patients under chlorpromazine treatment during swimming for physical therapy (68). Krähenmann (73) dealing with anesthesia of large domestic animals in the tropical climate of Khartoum, noticed that in general lower doses of chlorpromazine and promazine were required for horses than in the temperate climate of Zurich. This is in agreement with small animal experiments (9). Irvine (63) observed a patient of 84 years with generalized spasticity who was given 10 mg of diazepam intravenously daily for a week. The mean temperature of the ward was 18.5°C. After 7 days the daily dose was reduced to 2 mg per os. Ten days after admission the evening T_b of the patient was 29.4°C and never rose above 32.8°C during the following week until his death. Irvine concluded that "this patient was undoubtedly predisposed to accidental hypothermia by immobility and severe cerebrovascular disease, but it may be that diazepam was a contributory factor".

In a review on the effect of psychotropic drugs on body temperature Modestin (83) states that neuroleptica can affect body temperature and cause either hyperthermia or hypothermia and that among several factors ambient temperature plays a part. Lareng et al (74) compiled 17 cases where hypothermia and intoxication were found because of prolonged exposure to cold or cool ambient conditions after phenothiazines, barbiturates, and tranquilizers.

Reports on change of "body temperature" with neuroleptica treatment must be considered with caution. Harder et al (48) and Blum & Mauruchat (10) based

their findings on measurements of axillary temperature in resting draped patients. This indicates litttle more than a warming up of the body shell, possibly due to impairment of heat loss.

Cares et al (14) who investigated the effects of chlorpromazine in 3,014 hospitalized cases measured T_{re} and found "fever" in 0.8% of cases. T_{re} was usually below 38.3°C which is only a mild hyperthermia.

Of interest are experimental investigations of healthy individuals such as those by Iisalo et al (62) in a Finnish sauna at 80° and 93°C and 20–40% RH. The subjects were given propranolol and guanethidine. The rise of T_{or} after these drugs was not different from that after placebo. Propranolol had an inhibiting effect on the heart rate and the blood pressure. Iampietro et al (61) studied the effect of meprobamate (800 mg) on 36 healthy young men during 3½ hour exposure in a resting position at 10°C (cold), 27°C (thermoneutral), and 43°C (hot). There was no interference with temperature regulation at thermoneutral conditions. Heat production and core temperature were lower with the drug in the cold than in the placebo group, while only a moderate elevation of core temperature was found in the heat. Downey & Frewin (32) investigating the resting hand blood flow and the constriction of the blood vessels in the cold did not find any difference between patients in a mental hospital on continuous chlorpromazine treatment and normal subjects.

No change in body temperature was found in man taking various marihuana derivatives (59). An effect of heat should be anticipated after the administration of sympathomimetic drugs such as amphetamine, as physical activity and heat production increase while heat loss decreases due to peripheral vasoconstriction. Ginsberg et al (43) reported the case of a young man with amphetamine intoxication who showed signs of heatstroke with severe hyperthermia (T_{re} 42.5°C). The day or month of the year are not mentioned, nor are the thermal conditions. In this case, the patient was cooled in an icebath as a therapeutic measure. This is in agreement with what has been learned from experiments on animals (49).

Sympathomimetic drugs are sometimes taken by athletes to improve performance in competition. The action of the drug, if superimposed on heat production from muscular work, might be particularly dangerous in a hot climate or with intense heat load from solar radiation during the race. However no case has been reported in papers on doping (28).

Hyperthermia caused by infections or drugs in the heat may be critical if additional drugs are given. McGuigan (81) found an increased sensitivity to digitalis in pyrexic patients. For each degree centigrade rise of T_b there was a 10–15% increase of toxicity of digitoxin and digoxin above T_a 30°C in rats (72).

It has been known for a long time that ethyl alcohol intoxication is enhanced in the heat. Alcohol diminishes the reactivity of the peripheral blood vessels to cold (32), which results in an increased heat loss, while metabolic rate increases (47). This protects the body from hypothermia during a short cold exposure but not a prolonged one. Among their cases of accidental hypothermia Lareng et al (74) mention one of ethanol intoxication.

Topical Drug Administration

There are very few reports about the effect of temperature on topical drug administration. Cummings (24) applied N-octylamine, a histamine releaser, to the volar surface of the forearm of army volunteers at T_a 2°, 18°, 35°, and 45°C. The hands and bodies of the subjects were protected with clothing and blankets in the cold while they wore underpants in the heat. The rate of penetration of the compound increased with T_a and concentration as judged by wheal formation and erythema. A maximal cutaneous dilatation was recorded at 35° and 46°C. Cummings (24) also refers to other investigations that show improved drug absorption with increasing temperature of the skin and subcutaneous tissues. Becker et al (8) injected test doses of epinephrine and pilocarpine subcutaneously into the forearm in children and measured the response of the blood pressure. The resulting curves were correlated with weather conditions. Epinephrine increased blood pressure more rapidly in warm weather. Skin temperature was not measured. The authors suggested that the difference in response resulted from the influence of the weather. It could also have been that the absorption time in cold and warm weather was different.

The significance of skin temperature for blister formation when suction was applied in normal subjects was demonstrated by Peachey (89). Suction blister formation on the volar forearm increased with skin temperature in the range from 34° to 40°C.

Conclusion

The present knowledge of the effect of temperature on drugs shows that the toxicity of a great many drugs, particularly those with central effects, is influenced by the thermal environment. These effects are still very little understood. They are closely linked with the adaptation of the metabolism and physical and behavioral temperature regulation to the ambient. Where behavioral temperature regulation can be largely eliminated as in animal experiments, these effects are impressive; where behavioral temperature regulation is still fully or partially operative as in man, these effects are sparse and mild.

Most animal experiments are carried out between 15° to 33°C, which constitutes little temperature stress if means for behavioral temperature regulation are provided (112, 113). This is also the temperature range in which many large human population groups live, particularly in the industrialized countries of the temperate zone. It is to be expected that more knowledge on man will be accumulated if the heat exchange between man and the environment is more carefully considered. Wherever the adapting mechanisms are disturbed or paralyzed through a drug or while a drug is given, abnormal effects from the ambient can be anticipated.

Acknowledgement

Much help in the literature search for this review was received from the Library of the Division of Vitamin and Nutrition Research, F. Hoffmann-La Roche & Co. Ltd. Basel, and the Documentation Center of the Swiss Academy of Sciences, Bern, which is gratefully acknowledged.

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