Function of Vascular Counter-Current Heat Exchanger in Pyrogen Induced Fever. (29104)

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The biphasic or "2-step" increase in temperature of pyrogen induced fever in rabbits has been repeatedly observed(1-4) but not adequately explained. A change in the balance between rates of heat production and heat loss is the only mechanism by which temperature can be altered and studies have been confined to observations on the time courses of these 2 parameters. Skin temperature, usually that of the ear, has been used as an indication of peripheral blood flow and hence heat loss. Occasionally, skin temperature falls rapidly with onset of fever and remains level during the secondary rise in body temperature. It seems that this rise can only be brought about by an increase in heat production. However, heat exchange between arterial and venous blood could conserve body heat and play a part in determining the pattern of fever.

Heat exchange between arterial and venous blood has been demonstrated to exist by a number of investigators since the time of Claude Bernard(5). Bazett(6) described the exchanger principle and Scholander(7) has given excellent examples in specialized animal structures. A recent study(8) in this laboratory made it possible to evaluate this function on the basis of heat economy.

The present paper describes the heat production and heat loss patterns of rabbits given intravenous injections of purified bacterial endotoxin. The results suggest that a system of counter-current heat exchange, demonstrated to be present in the ear, may reinforce the effects of increased heat production and be responsible for the secondary rise in body temperature.

Methods. Experiments were conducted with male New Zealand White rabbits weighing 3 to 3.5 kg. They had been trained to sit throughout an experiment in a canvas sling with a wooden neck-stock. In 5 unanesthetized rabbits, determinations were made at several-minute intervals of blood flow to the ear, continuous rectal temperature, ear skin temperature, and heat loss from the skin, following i.v. injection of 0.2-6 μg/kg of a bacterial pyrogen. The pyrogen employed was a purified bacterial polysaccharide (endotoxin) obtained from *Salmonella abortus equi* and provided through the courtesy of Dr. Otto Westphal from the Dr. A. Wander Forschungsinstitut. Because of the development of tolerance, repeated injection was never tried into the same animal. The animals were kept at 26°C during and for more than a month prior to the experiments.

Unless otherwise mentioned, the techniques employed by Honda *et al*(8) were followed for the measurements of physiological parameters. In most cases, however, rectal temperature was recorded by the use of a thermistor probe (Yellow Spring 401) connected to a Sanborn carrier preamplifier with an adaptor (Bridge model 760-53). The heat flow disc used was made of a thin plastic sheet (35 × 35 × 1.5 mm) mounted with a series of 36 pairs of copper-constatan thermocouples: sensitivity (1 mV = 3.8 cal/cm^2/min).

Oxygen consumption, indicating heat production, was estimated by an open circuit method similar to that used by Hart *et al* in humans(9). Air was drawn through a hood covering the rabbit's head at a rate of 7 l/min and an aliquot of 100 ml/min was drawn off into a Beckman oxygen analyzer (sensitivity: 0.005%). In this way, the basal oxygen consumption (S.T.P.D.) averaged 432.3 ± 54.2 ml/kg/hr (± = 1 standard deviation).

Calculations. Symbols used. A = total area of skin surface of the ear (cm^2); F = ear blood flow (ml/min/100 ml tissue); H_1 = total heat loss by arterial precooling through the ear and its related part (cal/

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min); H_2 = total heat loss from surface of the ear (cal/min); $Q = H_2/A$(cal/min/cm^2); r = surface volume ratio of the ear (A/V) for which is substituted a value of 5.6 cm^{-1}; p = blood density for which is substituted a value of 1.06 g/ml; s = specific heat of blood for which is substituted a value of 0.8 cal/g/°C: T_a = ear arterial temperature (°C): T_r = rectal temperature (°C): T_s = ear skin temperature (°C): T_v = ear venous temperature (°C): and V = total volume of the ear (ml).

Heat which arterial blood loses as it flows from the interior to the surface of the ear is expressed as follows:

$$H_1 = sp(T_r - T_a)\, F(V/100) \quad (1)$$

Heat loss from the surface approximately equals heat loss from blood during its passing from arterial side to venous side in the skin. Thus,

$$H_2 = sp(T_a - T_v)\, F(V/100) \quad (2)$$

or

$$QA = sp(T_a - T_v)\, F(V/100)$$

$$T_a - T_v = (100rQ)/(spF)$$

$$T_a - T_v = 660\,(Q/F) \quad (3)$$

The relative activity of two kinds of heat exchangers, H_1/H_2, can be taken as indices of the function of the countercurrent heat exchanger, and it readily follows from Equations 1 and 2:

$$(H_1/H_2) = (T_r - T_a)/(T_a - T_v) \quad (4)$$

$$= (T_r - T_v)/(T_a - T_v) - 1$$

By substituting $T_a - T_v$ given in Equation 3 for the above equation the following is obtained:

$$(H_1/H_2) = (1/660)\,(T_r - T_v)\,(F/Q) - 1$$

or

$$(H_1/H_2) = (1/660)\,(T_r - T_s)\,(F/Q) - 1 \quad (5)$$

This derivation assumes that venous temperature, T_v, equals skin temperature, T_s.

Results. After an initial latency of about 15 to 60 minutes there was an increase in rate of heat production which was associated with tremors over the limbs and body similar to shivering. Heat production rose rapidly to a maximum of about +90% (range 74-108) of preinjection levels and then fell remarkably to about +25% after about 30 minutes where it remained for approximately

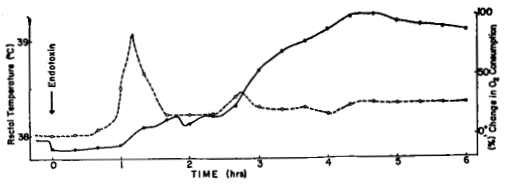

FIG. 1. Rectal temperature (○) and oxygen consumption (●) of a rabbit after i.v. injection of 2 μg/kg endotoxin. Oxygen consumption at 0 change = 372 ml/kg/hr (S. T. P. D.).

the next 5 hours (Fig. 1). Body temperature increased by two steps. The first step was a small increase of about 0.3 to 0.5°C soon after the initial burst of increased heat production. This increase was followed by a period during which there was little or no change in temperature. The secondary rise of about 1°C, usually took place 2 to 3 hours after injection of the pyrogen and at a time when heat production had fallen to +25% for about one hour.

The changes of the 3 parameters, F, Q, and T_s were almost in the same direction. The initial rising phase of T_r was associated with decreased heat loss (Q). However, the secondary rise in T_r occurred at a time when heat loss was constant (Fig. 2).

The function of the counter-current heat exchanger, H_1/H_2, calculated from the values for T_r, T_s, F and Q according to equation 5, is plotted in Fig. 2. This function rose late during the first rising phase (5 out of 5 trials: significant statistically at $P<0.05$) of

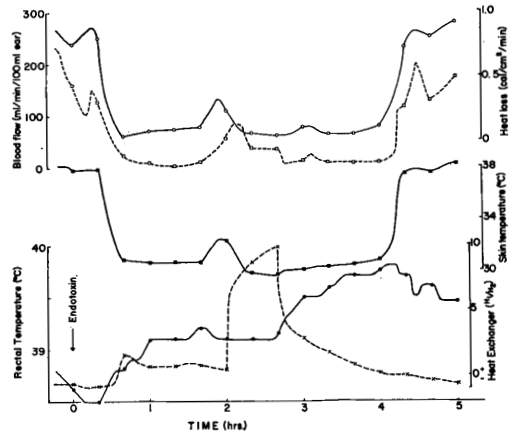

FIG. 2. Ear heat loss (○), blood flow (□), skin temperature (■), heat exchange function (×) and rectal temperature (●) of a rabbit after i.v. injection of 2 μg/kg endotoxin.

the fever and fell just before the peak in rectal temperature was reached.

Associated with the decline in rectal temperature about 4 to 5 hours after the injection of endotoxin was a vasodilatation and increased heat loss from the ear.

Discussion. The term "biphasic" has often been used to describe the pattern of pyrogen fever; however, this does not mean 2 independent peaks which are of the same type and size. Whatever the underlying mechanism(2,3,4) may be, this fact is one important aspect of the problem.

The body temperature of the rabbits started to rise soon after the increase in general heat production and the reduction in heat loss from the ears occurred. Thus the initial rise in rectal temperature can be adequately accounted for. The response of heat production was similar to that described for man(10) but different from a previous experiment using typhoid-paratyphoid vaccine (1). The secondary rise in temperature occurred at a time when heat production was only +25% and heat loss, as judged from the ear, was constant. This rise in rectal temperature could have been brought about by the onset of vasoconstriction in other areas. However, the main region of heat loss in rabbits is from the ears and it seems unlikely that other regions could play a significant part. The close correlation between rectal temperature changes and heat loss changes from the ears at the beginning and end of the experiments suggests that the ear is a good indicator of the overall heat loss pattern of the animal.

During the initiation of fever, the value is lowered for F/Q and accordingly for H_1/H_2. Later both Q and T_s decrease and T_r increases to some extent, and H_1/H_2 is elevated. Next, when $T_r—T_s$ is still large, F starts to increase, thus H_1/H_2 is further elevated after the first peak.

Immediately before or at the beginning of the second rising phase, the value for T_r is not as small as the control value and usually the value for T_s is not as large. In addition, the value for F/Q is not lowered because the rate of change in F is rather slow and thus Q does not follow F. Accordingly, the values for H_1/H_2 can be large throughout the second rising phase. On the other hand, on physical grounds Q is expected to be large even with the same value for F in case T_r is large. This may be the reason why H_1/H_2 values cannot be as high after the second peak is over.

The rise in H_1/H_2 ratio that occurs just before the secondary rise in T_r suggests that this increase may be due to increased amount of heat recovered by the core. The fact that heat loss from the ear remains constant while the body temperature is higher indicates that this is occurring.

Bazett(6) stated that the warmed venous blood leaving the muscle should be cooled by the close contact with the out-flowing arterial blood during shivering. In the goat, blood temperature may exceed rectal temperature in this period(11). This may be an additional factor in the small value for H_1/H_2 in this phase of fever. Pyrogen induced fever in curarized dogs has been related to vasoconstriction(12). However, in the present experiments heat production by shivering appears to contribute to the initiation of fever.

Summary. The initial rise in pyrogen induced fever in rabbits can be accounted for by the increase in heat production and decrease in heat loss. The secondary rise can be attributed to increased amount of heat recovered by the core through counter-current heat exchanger.

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Effects of a Tranquilizer on Body Temperature. (29105)

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Since the mechanisms of body temperature regulation of homoiotherms are characteristically altered or ablated by the effects of general anesthetics(1), studies of thermal control are better performed on unanesthetized animals. The recent development of a variety of tranquilizers [pharmacological agents which reduce activity and agitation and make subjects more docile(2)] makes available a group of materials offering the hope of obtaining quiescent animal preparations retaining thermoregulatory ability. Earlier studies have investigated some of these materials as they produce changes in behavior(3,4,5), physiology(6,7,8), or to a more limited extent temperature regulation (9,10,11,12) in various species. The present program was designed to determine the effects of propiopromazine hydrochloride (Tranvet, Abbott Laboratories) on thermoregulatory ability in dogs exposed to 3 environmental temperatures.

Methods. Forty-eight 2-hour experiments were conducted using 4 young, adult mongrel dogs (11.5 to 16 kg) each exposed twice to 3 environmental temperatures: 4.4°C (40°F), 23.9°C (75°F, and 37.8°C (100°F), at 50% relative humidity, without the use of a tranquilizer and twice to each temperature tranquilized with 2.2 mg/kg propiopromazine (intravenously). No animal was given tranquilizer within 48 hours of a previous injection. All animals were placed in the environmental chamber with body temperatures elevated by moderate exercise to force regulation and to provide more comparable initial rectal temperatures within the group. The animals were unrestrained, but were restricted to a small area by a collar and a short rope. Rectal temperature was continuously monitored by a thermistor probe inserted 10 cm into the lower colon and recorded on a Grass Polygraph Recorder (model 5C) through an appropriate bridge.

In addition to the above experiments, one animal was exposed to each of the environmental temperatures without prior exercise to indicate the influence of this single variable on internal body temperature.

Results. During a 2-hour exposure to an ambient temperature of 23.9°C, untranquilized animals fell from the average initial temperature of 39.23°C to 38.31°C (—0.92°C) and tranquilized animals decreased rectal temperature from (39.15°C to 38.15°C) (—1.00°C) in the same period (Fig. 1A).

At 37.8°C rectal temperatures of the tranquilized animals rose from 39.35°C to 39.61°C (+0.26°C), while the untranquilized group dropped rectal temperature from 39.44°C to 38.88°C (—0.56°C) (Fig. 1B).

At 4.4°C the tranquilized dogs dropped internal temperature from 39.32°C to 38.25°C (—1.07°C) in 2 hours with a low temperature of 38.02°C (—1.30°C) reached at 80 minutes. The control animals, with an initial temperature of 39.04°C demonstrated regulation at a level of 38.60°C (—0.44°C) after