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Oxygen Consumption and Body Temperature of Newborn Rabbits during Recovery from Hypothermia Developed under Various Experimental Conditions

By

GY. MESTYÁN

Department of Paediatrics, University Medical School, Pécs
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In premature and full-term infants hypothermia does not alter the thermoneutral zone, which is identical with that of normothermic premature infants. This has convincingly been demonstrated by the observation that subnormal deep body temperature in infants kept at 34—36 °C is not accompanied by an increased O_2 consumption, which points to the important role of cutaneous thermoreceptors in regulation of heat production [3, 9, 10]. In the light of this observation the question arises whether the same relationship between O_2 consumption and body temperature exists at neutral temperature in newborn animals whose body temperature falls considerably on exposure to cold. The "immature" newborn rabbit appears to be a suitable model for studying the question. In earlier investigations [2] it was observed that in thermoneutral environment hypothermia was associated with an O_2 consumption higher than the minimal metabolic rate. Thus, in contrast to premature infants, in the newborn rabbit the thermal state of the core of the body seems to play some role in the control of heat production.

In addition to the relationship of body temperature and the metabolic response to cold, the relationship between minimal O_2 consumption and body temperature has been studied in newborn rabbits with severely impaired chemical thermoregulation. Anaesthesia, the administration of various drugs (hexamethonium, neuromuscular blocking agents) and various experimental procedures sometimes abolished the metabolic response to cold, which rendered the animal suitable for studying a possible direct relationship between body temperature and energy metabolism. The observations to be reported have undoubtedly confirmed the conclusion drawn from investigations performed on adult animals and premature and full-term infants that a fall in body temperature is not accompanied by a decrease in minimal metabolic rate as one would expect if the metabolic rate conformed with van't Hoff's law.

METHODS

Observations were made on unanaesthesized and anaesthesized newborn rabbits. The details of the method and its modifications according to the various experimental procedures have been described previously [16].

The advantage of the apparatus used was that small modifications and, by attaching a tracheal cannula of small dead space to an external closed circuit of about 130 ml volume, tidal air and respiratory rate could also be recorded. In some cases respiration was paralyzed by means of d-tubocurarine or gallamine. In these experiments the partially immobilized animal was placed in a cylindrical transparent perspex chamber, and negative pressure ventilation was applied by means of a Starling pump. The perspex chamber containing the animal was suspended in a water-bath. When the temperature of the water-bath was abruptly altered the air temperature within the respiration chamber reached its new equilibrium in about 10 min.

Mean blood pressure was recorded from a carotid artery by means of a capacitance manometer. For general anaesthesia urethane was injected intraperitoneally or sometimes intravenously in a dose of 0.5 to 1.5 g/kg. Hexamethonium was given subcutaneously or intraperitoneally in a dose of 10—20 mg/kg, and in some cases intravenously in a dose of 10 mg/kg.

Results and Discussion

Body temperature and O_2 consumption of unanaesthesized newborn rabbits during recovery from hypothermia in a thermoneutral environment

At the beginning of the examinations concerning the regulation of respiratory metabolism of newborn rabbits, O_2 consumption at neutral temperatures was found to be considerably greater than the expected minimal metabolic rate. Continuous recording of rectal or colonic temperature revealed that the unusually high minimal O_2 consumption was always accompanied by a low core temperature. With rising body temperature O_2 consumption fell gradually to the minimal level. Fig. 1 shows O_2 consumption of a 2-day-old rabbit, in a neutral environment, at 2 minute intervals. Recording was started 10—15 minutes after the animal had been placed in the perspex chamber, when the new equilibrium was reached.

During a period of 15 minutes after the measurements had begun O_2 consumption was high and did not change appreciably, then it fell rapidly but further 20 minutes were necessary to reach the basal level.

Simultaneous recording of O_2 consumption, and rectal and colonic temperature undoubtedly showed that hypothermia was responsible for the increased energy metabolism at the neutral ambient temperature. The relation of changes in body temperature and O_2 consumption in 2 hypothermic newborn rabbits during rewarming at an environmental temperature of 35 °C is shown in Fig. 2. The close correlation of changes in the two parameters is quite obvious. During the first 15 minutes, respiratory metabolism was considerably above the minimal level (an increase of 100 to 150 per cent), while the low rectal temperature rose rapidly to 36—37 °C. The raised O_2 consumption approximately corresponded to the level obtainable on exposure to 25—27 °C of a newborn rabbit.

During the further course of recovery from cold exposure, when the rise in body temperature proceeded at a slower rate than before, it took 30 minutes for O_2 consumption to the cold environment to an ambient temperature of 35—37 °C. All rabbits showed a metabolic response to cold accompanied by a fall in rectal temperature. It is obvious from the dia-

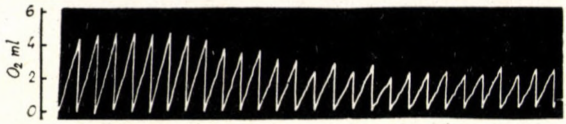

FIG. 1. O_2 consumption in a 2-day-old rabbit weighing 85 g at 2 minute intervals during recovery from hypothermia in a thermoneutral environment

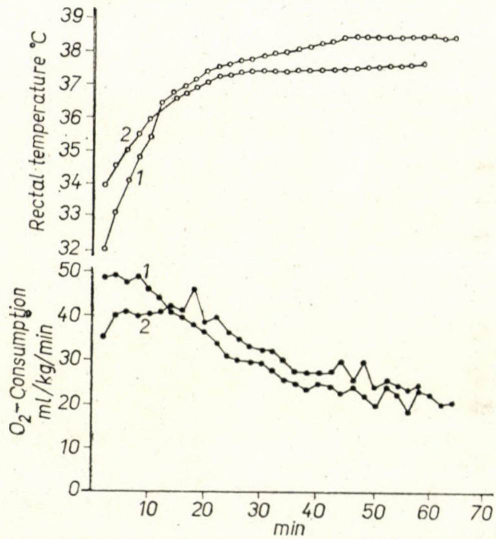

FIG. 2. 1) O_2 consumption (●) and body temperature (○) of a 2-day-old rabbit weighing 65 g. 2) O_2 consumption (●) and body temperature (○) of a 1-day-old rabbit weighing 55 g during rewarming at an ambient temperature of 35°C

reach the minimal value. In fact, metabolic rate at a rectal temperature of 37.3 °C in animal No. 2 and of 38 °C in animal No. 1 was still higher than the basal metabolism.

In Fig. 3, O_2 consumption of 10 rabbits less than 6-day-old is plotted against rectal temperature, showing the relationship of these two parameters after returning the animals from gram that the reduced body temperature exerted a metabolic effect in the warm environment. All animals maintained a raised O_2 consumption for periods of half an hour or more when returned in the neutral environment.

O_2 consumption did not even start to decline before rectal temperature had reached 36 °C or more.

There are two conclusions to be drawn from these observations. First, considerable care must be taken when determining minimal O_2 consumption in newborn animals, to ensure that they have really attained their temperature equilibrium in the neutral thermal environment; there is a danger that the metabolic rate may be overestimated. Second, it would seem that even the temperature gradient across the skin is reversed on placing a newborn rabbit with a rectal temperature of 32—34 °C in a chamber at 35 °C, the low body temperature constitutes an adequate stimulus to increase O_2 consumption. This is in contrast with the observations on premature and full term babies, in whom a reduced body temperature within the thermoneutral zone is not accompanied by an increased metabolic rate.

Minimal O_2 consumption and body temperature of newborn rabbits with severely impaired thermoregulation in a thermoneutral environment

Various experimental procedures (anaesthesia, artificial ventilation, hexamethonium treatment, immobilization) carried out in newborn rabbits often abolished the metabolic response to cold which resulted in a considerable fall of body temperature. The profound hypothermia unaccompanied by an increase in heat production allowed to study the relationship between body temperature and minimal O_2 consumption within wide body temperature ranges after exposure to

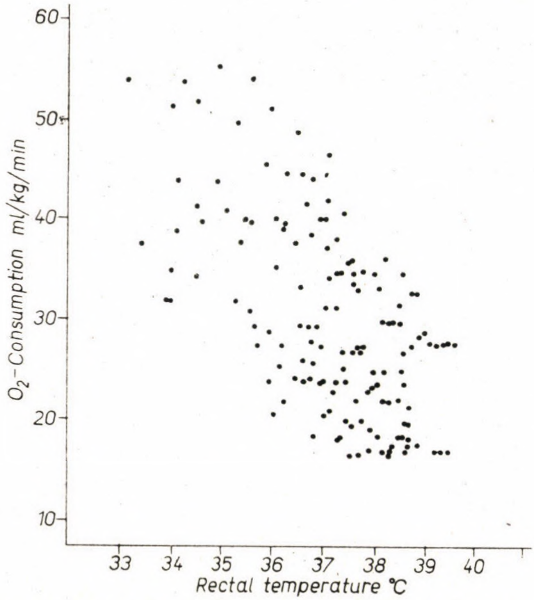

FIG. 3. O_2 consumption in ten rabbits aged 1 to 6 days, in relation to rectal temperature, during recovery from hypothermia at a neutral temperature

cold and during recovery from hypothermia in a thermoneutral environment.

Fig. 4 demonstrates results obtained in newborn rabbits which did not show a metabolic response to cold. It can be seen that over a temperature range from 32 to 38 °C at any given rectal temperature the rate of O_2 consumption was practically the same, and no significant changes occurred during cooling or rewarming. From

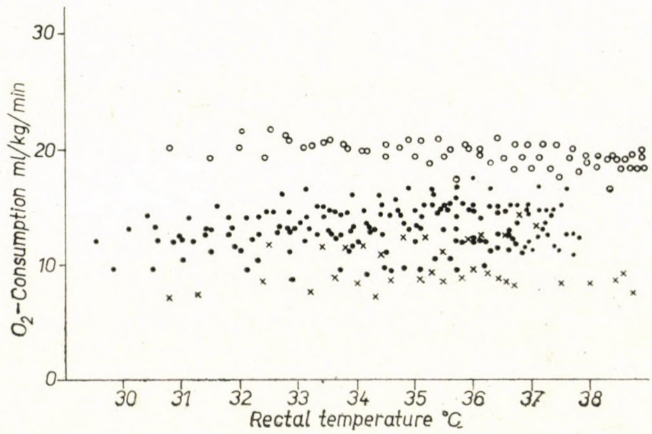

FIG. 4. O_2 consumption in 11 rabbits aged 1 to 11 days, in relation to rectal temperature in the course of rewarming in a thermoneutral environment. None of rabbits showed a metabolic response on exposure to cold. ○ = partial immobilization + tubocurarine, × = partial immobilization + hexamethonium, ● = partial immobilization + urethane

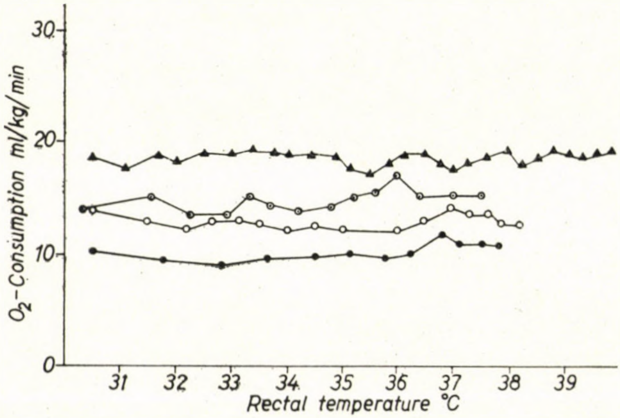

FIG. 5. O_2 consumption in 4 newborn rabbits with severely impaired chemical thermoregulation, as a function of body temperature. ▲ = age: 10 days; body weight: 130 g. Anaesthetized with urethane and paralyzed by tubocurarine, ⊙ = age: 4 days; body weight: 75 g. Immobilized, and anaesthetized with urethane, ● = age: 1 days; body weight: 65 g. Immobilized, and anaesthetized with urethane, ○ = age: 5 days; body weight: 63 g. Immobilized, and anaesthetized with urethane

these observations it follows that in the absence of chemical thermoregulation a change in body temperature does not affect minimal metabolism. It should be noted that the various experimental procedures and condi-

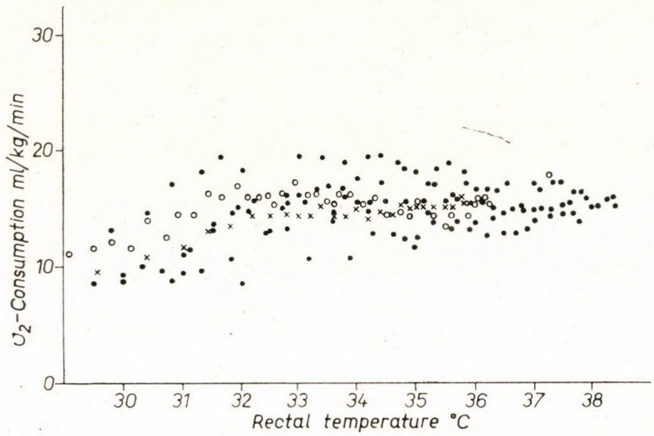

FIG. 6. O_2 consumption in 3 to 10-day-old rabbits in relation to their body temperature during recovery from hypothermia at an ambient temperature of 35°C. No increase in O_2 consumption occurred on exposure to cold. ○ = urethane + tubocurarine + immobilization, × = urethane + hexamethonium + immobilization, ● = urethane + immobilization

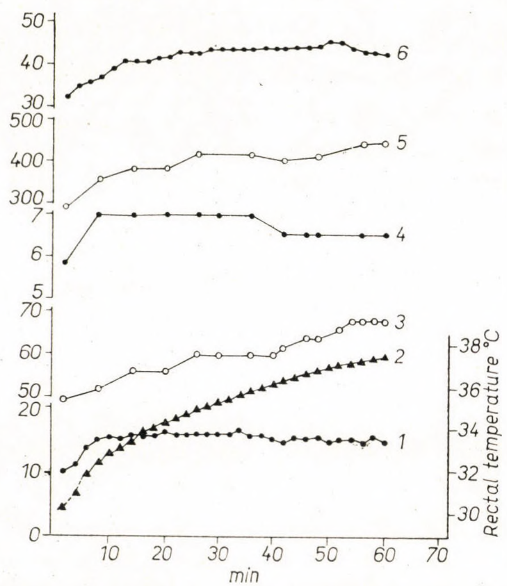

FIG. 7. Recovery from hypothermia in a 10-day-old rabbit weighing 115 g, anaesthetized with 1 g/kg urethane and immobilized. Ambient temperature, 35 °C. 1. = O_2 consumption ml/kg/min, 2. = body temperature, 3. = respiratory frequency min, 4. = respiratory volume ml/kg, 5. = respiratory minute volume/kg, 6. = mean blood pressure mmHg

tions may substantially decrease minimal O_2 consumption, but cooling or rewarming, despite the considerable changes in the thermal state of the body, does not alter the new level of the basal metabolic rate. These observations are consistent with those made in adult rats in which the metabolic response to cold had been abolished by bilateral hypothalamic lesion [12, 13, 14]. These animals were able to maintain a normal or subnormal basal metabolic rate over a wide range of body temperature, and thus no Q_{10} effect could be observed.

A body temperature lower than 32 °C was sometimes found to be associated with a low minimal metabolic rate (Fig. 6), and at the beginning of recovery at 35 °C ambient temperature, O_2 consumption increased gradually until a body temperature of 31.5 to 32 °C had been reached. During the further course of rewarming, O_2 consumption remained unchanged at that higher level. In such animals, as has previously been found in damaged premature infants, rewarming sometimes caused an abrupt rise in minimal metabolism at about the same body temperature (31 to 32 °C). The findings in such a newborn rabbit are shown in Fig. 7. In this experiment, in addition to O_2 consumption and body temperature, respiratory rate and volume and mean blood pressure were recorded. It can be seen that below a body temperature of 32 to 33 °C not only O_2 consumption but the other parameters were also reduced. While, on rewarming, metabolic rate, respiratory volume and blood pressure soon rose to a higher level, respiratory frequency and to a certain extent respiratory minute volume increased steadily throughout the recovery period.

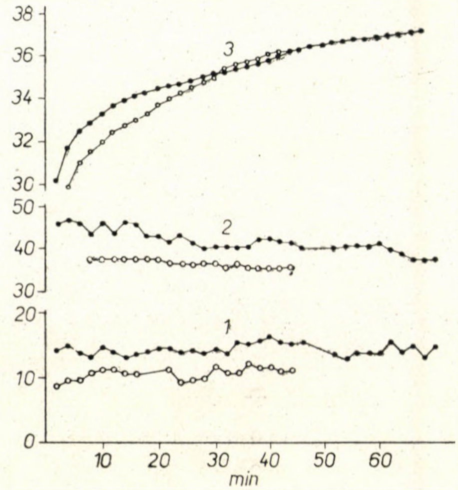

FIG. 8. O_2 consumption, colonic temperature and mean blood pressure during rewarming in a thermoneutral environment. The animals were anaesthetized with urethane (1g/kg) and immobilized. ● = 4-day-old rabbit weighing 75 g, O = 5-day-old rabbit weighing 80 g. 1) O_2 consumption ml/kg/min. 2) Mean blood pressure mmHg 3) Rectal temperature °C

The close relationship and parallel changes of these physiological parameters occurred regularly under various experimental condition.

In Fig. 8 two experiments are illustrated in which neither O_2 consumption nor mean blood pressure was reduced at a body temperature lower than 32 °C. On the contrary, in one animal rewarming caused a fall in mean blood pressure from 45 mm Hg to 37 mm Hg.

The rule of van't Hoff refers to the relationship between the change in O_2 consumption rate and the change in temperature, which is expressed by the formula $Q_{10} = \frac{k(t+10)}{kt}$. A 10 °C rise in temperature has been found to cause a 2—3 fold increase in the reaction velocity. The formula has been used in describing the effect of temperature upon functions or processes of biological systems, and the same quantitative relationship has been found. The incorrect application of van't Hoff's prediction in living homoiotherm organisms led to the wide acceptance of a direct linear relation between body temperature and heat production. This concept does not take into consideration that even the Q_{10} of quite a number of simple biochemical processes does not conform with van't Hoff's rule, and its value may change substantially over wide temperature ranges. An even more complicated situation arises when one is attempting to attribute to van't Hoff phenomenon the changes in metabolism of a living organism recorded at different body temperatures.

It became apparent from a series of studies performed on adult rats by DONHOFFER et al. [6, 7, 8] that precaution should be taken in applying the Q_{10} effect to describe the parallel changes in body temperature and O_2 consumption as a cause and effect relationship in the homoiothermic animal. It has been shown, among others, that the increase in heat production associated with hypothermia is not a direct consequence of the rise in body temperature. Essentially the same conclusion has been reached concerning the relation of body temperature to O_2 consumption in hypothermia caused by exposure to cold after chemical thermoregulation had been abolished by bilateral hypothalamic lesions and local heating of the hypothalamus [11]. It follows that under certain conditions considerable changes in body temperature may occur without a notable change in minimal O_2 consumption. The rule of van't Hoff has in addition been applied to explain the changes in energy metabolism observed in newborns exposed to various temperatures. Thus the postnatal rise in minimal O_2 consumption has been partially or totally attributed to the simultaneous rise in body temperature [1, 4, 16, 17, 18]. Our own studies in premature infants revealed no correlation between colonic temperature and minimal O_2 consumption. This has been confirmed in full term infants by ADAMSONS et al. [2]. Recently, SCOPES [19] has reported on the occurrence of a Q_{10} effect in newborn infants aged less than 6 hours, but in babies older than 6 hours no such correlation was found. However, even the best correlation conforming with van't Hoff's prediction does not justify to infer that the observed changes in heat production are directly related to the changes in body temperature.

Observations in damaged newborn infants with severely impaired chemical thermoregulation have shown that not only a fall in body temperature of 2 to 3 °C but also one of 4 to 7 °C does not affect minimal O_2 consumption

[15]. In hypothermic damaged infants exhibiting a very low basal metabolic rate, rewarming to 32 to 32.5 °C occasionally caused an abrupt increase in O_2 consumption which thereafter persisted at this new level.

All these observations already suggested that the absence of the metabolic response to cold does not necessarily render the adult animal or the newborn infant poikilothermic in the sense that the metabolic rate would be dependent solely upon body temperature. The existence of additional control mechanisms by which minimal metabolism, either normal or subnormal, is maintained in spite of considerable changes in body temperature, has strongly been supported by the present observations in newborn rabbits whose metabolic response to cold has been abolished. Just as in the adult animal or the premature infant, in newborn rabbits with impaired thermoregulation, a change in body temperature of 8 to 10 °C, either during cooling or rewarming, has failed to exert a Q_{10} effect upon O_2 consumption. The maintenance of normal or subnormal basal metabolic rate within a surprisingly wide range of body temperature also points to a mechanism involved in the control of minimal metabolic rate whose nature and function remains to be elucidated.

Summary

The relationship of O_2 consumption and body temperature in unanaesthesized and anaesthesized newborn rabbits during recovery from hypothermia in a thermoneutral environment has been investigated.

(i) O_2 consumption of normal rabbits depended upon the thermal state of the body; a core temperature lower than 38 °C was accompanied by an increase in O_2 consumption. It appears that a reduced body temperature has some importance in eliciting an increase in heat production.

(ii) In rabbits with severely impaired chemical thermoregulation no Q_{10} effect upon O_2 consumption could be observed in the temperature range from 32 to 38 °C.

(iii) In addition to the severely impaired chemical thermoregulation, various experimental procedures and conditions may lower the level of minimal O_2 consumption, but neither a considerable rise nor a fall in body temperature caused such a change in the new level of metabolism as one would have expected on the basis of van't Hoff's law. The existence of a control mechanism is suggested by which minimal O_2 consumption, either normal or subnormal, is maintained in spite of considerable changes in the thermal state of the body.

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Dr. Gy. Mestyán
Gyermekklinika
Pécs, Hungary