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Review

Perinatal adaptation in mammals: The impact of metabolic rate ☆

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Abstract

Mammalian birth is accompanied by profound changes in metabolic rate that can be described in terms of body size relationship (Kleiber's rule). Whereas the fetus, probably as an adaptation to the low intrauterine pO_2, exhibits an "inappropriately" low, adult-like specific metabolic rate, the term neonate undergoes a rapid metabolic increase up to the level to be expected from body size. A similar, albeit slowed, "switching-on" of metabolic size allometry is found in human preterm neonates whereas animals that are normally born in a very immature state are able to retard or even suppress the postnatal metabolic increase in favor of weight gain and O_2 supply. Moreover, small immature mammalian neonates exhibit a temporary oxyconforming behavior which enhances their hypoxia tolerance, yet is lost to the extent by which the size-adjusted metabolic rate is "locked" by increasing mitochondrial density. Beyond the perinatal period, there are no other deviations from metabolic size allometry among mammals except in hibernation where the temporary "switching-off" of Kleiber's rule is accompanied by a deep reduction in tissue pO_2. This gives support to the hypothesis that the postnatal metabolic increase represents an "escape from oxygen" similar to the evolutionary roots of mitochondrial respiration, and that the overall increase in specific metabolic rate with decreasing size might contribute to prevent tissues from O_2 toxicity.

Keywords: Metabolic size relationship; Perinatal adaptation; Preterm neonates; Newborn marsupials; Hypoxia tolerance; Mammalian hibernation; Mitochondrial respiration; Oxygen toxicity

Contents

1. Introduction

Mammalian birth is characterized by the onset of lung breathing and by the subsequent transition from fetal to adult circulation. All these changes result in a marked improvement of oxygen supply and, thus, form the precondition for novel physiological functions with increased oxygen demand, such as thermoregulation. The transitional events occurring at birth are usually referred to as "perinatal adaptation". However, the

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mammalian neonate has not only to adapt to extrauterine life, but also to the risks involved in the birth process itself which, for instance, may lead to a temporary lack of oxygen. There is increasing evidence that the multimodal "adaptation" of mammalian neonates is closely connected to metabolic rate and can be described in terms of body size relationship.

The specific (mass-related) basal metabolic rate of mammals increases with decreasing body size (Fig. 1). The "allometric" (non-proportional) size relationship of metabolic rate, often referred to as Kleiber's rule (Kleiber, 1961), is traditionally explained by the fact that small mammals lose more heat through their relatively larger surface area and therefore need a higher internal "heating rate" to keep their body temperature constant (Rubner, 1883; White and Seymour, 2003). However, Kleiber's rule also holds true in poikilothermic animals (Hemmingsen, 1960; Schmidt-Nielsen, 1984) and deviates from the mathematical mass relationship to be expected in true surface proportionality (Heusner, 1982; Feldman and McMahon, 1983) so that it seems to have been a favorable precondition rather than a consequence of homeothermy (Singer et al., 1995; Singer, 2002). As the ultimate causes, other conditions such as the fractal structure of distributive networks (Sernetz et al., 1985; West et al., 1997, 2002) or the "cascade" of metabolic pathways interacting in rest and exercise (Darveau et al., 2002; Hochachka et al., 2003) are currently under discussion (Smil, 2000; Burness, 2002; Singer, 2006).

With respect to perinatal transition, it has long been known that the mammalian fetus exhibits an adult-like specific metabolic rate (behaves "like an organ of its mother") (Bohr, 1900; Hasselbalch, 1900; Wilkie, 1977; Wieser, 1984), with the increase up to the level to be expected from body size occurring only after birth (Fig. 2). The suppression of metabolic size allometry in mammalian fetuses (and avian embryos) reflects an adaptation to the limited oxygen transport capacity of the placenta (or egg shell, respectively) (Rahn, 1982; Paganelli and Rahn, 1984). In fact, the mean pO_2 in the fetal circulation amounts to only 25 mmHg ("Everest in utero"). Although this is partially compensated for by an elevated red cell count and by a left-shifted oxygen binding curve of fetal hemoglobin, it would

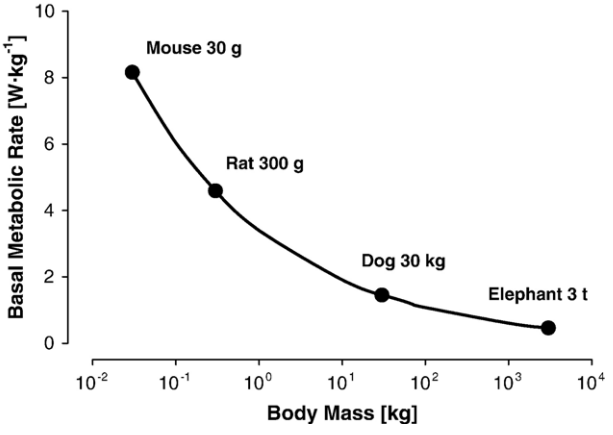

Fig. 1. Increase in specific basal metabolic rate with decreasing body size in mammals (metabolic size allometry, Kleiber's rule).

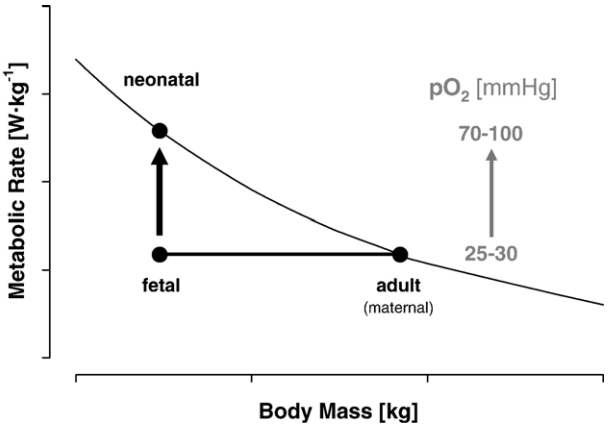

Fig. 2. Onset of metabolic size allometry in mammalian neonates. The "switching-on" of Kleiber's rule is accompanied by a marked increase in pO_2.

prevent oxygen from diffusing into the depth of tissues, unless the metabolic rate would be correspondingly low. Incidentally, the mammalian fetus (as well as the avian embryo) can "afford" the low metabolic rate from a thermoregulatory point of view as it is passively incubated at normal body temperatures by its mother.

2. Perinatal metabolic adaptation to immaturity

Whereas in term babies, Kleiber's rule is "switched-on" within a few hours, human preterm neonates undergo a more or less slowed increase in metabolic rate, depending on the degree of immaturity (Hill and Rahimtulla, 1965; Singer, 1998). Nevertheless, the size-adjusted metabolic rate is attained well before the originally expected date of birth. The slowed increase up to an "appropriately" high metabolic level contributes to the long-lasting thermal instability of small preterm neonates. However, the premature onset of metabolic size allometry means that their specific metabolic rate is eventually higher than it would have been in utero. Thus, preterm birth is characterized by a relative hypermetabolism which explains the delayed "catch-up" growth starting only after considerable increase in substrate supply (Fig. 3A).

In contrast, it has been shown that marsupial neonates that are normally born in an extremely immature state do not exhibit any increase in metabolic rate. Apparently, these "extrauterine fetuses" are able to suppress the postnatal onset of metabolic size allometry and to live on a "feto-maternal" metabolic level well below that expected from body size (Baudinette et al., 1988; Singer, 1998). This means that they remain poikilothermic, their body temperature being fully dependent on parental care. However, the low heat output rate is accompanied by an exponential increase in body mass. The metabolic reduction seems to provide these tiny neonates with a high growth efficiency in spite of a necessarily limited substrate supply (Fig. 3B). Moreover, it has been shown that, at least during the first few days of life, most part of their oxygen demand is met by skin respiration rather than by gas exchange through their extremely immature lungs (Mortola et al., 1999). Obviously, a