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NEONATAL THERMOREGULATION

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✓ ***Resume***

Once born, the neonate quickly cools down in response to the colder environment outside the womb, leading to a rapid drop in temperature. To survive, the neonate must generate heat rapidly through nonshivering thermogenesis (NST), which is linked to the breakdown of fat in brown adipose tissue. Heat is produced by uncoupling ATP synthesis through the oxidation of fatty acids in mitochondria, using uncoupled proteins.

Keywords: newborn, heat transfer, temperature.

ТЕРМОРЕГУЛЯЦИЯ НОВОРОЖДЕННЫХ

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✓ ***Резюме***

После рождения новорожденный быстро остывает в ответ на более холодную среду вне утробы, что приводит к быстрому понижению температуры. Чтобы выжить, новорожденный должен быстро вырабатывать тепло посредством непрерывного термогенеза (НТ), который связан с расщеплением жира в бурой жировой ткани. Тепло вырабатывается путем прекращения синтеза АТФ путем окисления жирных кислот в митохондриях с использованием несвязанных белков.

Ключевые слова: новорожденный, теплообмен, температура.

ЯНГИ ТУҒИЛГАН ЧАҚАЛОҚЛАРНИНГ ТЕРМОРЕГУЛЯЦИЯСИ

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✓ ***Rezyume***

Туғилгандан сўнг, чақалоқ бачадондан ташқаридаги совуқ муҳитга жавобан тез совийди, бу эса ҳароратнинг тез пасайишига олиб келади. Омон қолиш учун янги туғилган чақалоқ узлуксиз термогенез (УТ) орқали тезда иссиқлик ҳосил қилиши керак, бу жигарранг ёғ тўқималарида ёғнинг парчаланиши билан боғлиқ. Иссиқлик митохондриядаги ёғ кислоталарини боғланмаган оқсиллар ёрдамида оксидлаш орқали АТФ синтезини тўхтатиш орқали ҳосил бўлади.

Калит сўзлар: янги туғилган чақалоқ, иссиқлик узатиш, ҳарорат.

Relevance

The fetal metabolic rate per unit of tissue weight is relatively high compared to that of an adult. Additionally, heat is transferred to the fetus through the placenta and the uterus, resulting in a temperature 0.3℃ to 0.5℃ higher than that of the mother. Consequently, fetal temperature relies on maternal conditions until birth.

Thermogenesis needs to commence shortly after birth and persist for several hours. Since thermogenesis requires sufficient oxygenation, a distressed neonate with hypoxemia cannot produce enough heat to raise its temperature adequately. In contrast to neonates, fetuses cannot increase heat production. This is due to inhibitors of NST present in the placenta, which enter the fetal bloodstream. Key inhibitors include adenosine and prostaglandin E2, both of which have potent anti-lipolytic effects. These inhibitors are crucial for the metabolic adaptation of a physiologically hypoxic fetus, as NST necessitates adequate oxygenation. Moreover, the presence of NST inhibitors enables the fetus to accumulate sufficient brown adipose tissue before birth.

The umbilical circulation transfers 85% of the fetal heat production to the maternal circulation. The remaining 15% is dissipated through the fetal skin to the amnion and then transferred through the uterine wall to the maternal abdomen. As long as fetal heat production and loss are balanced appropriately, the temperature difference between the fetus and the mother remains constant (heat clump). However, when the umbilical circulation is obstructed for any reason, the fetal temperature will rise in proportion to the extent of the obstruction. In cases of acute cord occlusion, fetal temperature may reach hyperthermic levels, potentially impacting fetal growth and brain development. Experimentally induced cord occlusion, a significant cause of brain damage, results in a rapid increase in body temperature, although brain temperature tends to remain stable. This is considered a cerebral thermoregulatory adaptation to hypoxemia, providing physiological protection against hyperthermia, a condition that predisposes the fetus to hypoxic injury (cerebral hypometabolism).

The purpose: Fetuses undergo development within the uterus, benefiting from a relatively stable thermal environment. The maternal body consistently supplies an adequate amount of heat to the amnion via the placental surface and umbilical circulation, thus ensuring thermal stability within the intrauterine environment. Typically, fetal temperature is 0.3℃ to 0.5℃ higher than maternal temperature, suggesting that fetal thermoregulation is immature and heavily reliant on maternal temperature. However, central thermoregulatory mechanisms are already well developed before birth.

Following birth, the thermal environment undergoes significant changes. The ambient temperature in the delivery room, typically around 26℃ to 27℃, is approximately 10℃ lower than the intrauterine temperature. To survive this transition, newborns, whose thermoregulation was previously dependent on the maternal environment inside the uterus, must rapidly increase heat production. Mammalian newborns exhibit this response by elevating heat production within minutes after birth. This article provides an overview of fetal and neonatal thermoregulation as described above.

Much of the information discussed here stems from animal experiments, resulting in limited data from human fetuses and neonates. Nevertheless, understanding thermoregulatory adaptations in distressed or hypoxic human fetuses and neonates is crucial for clinicians, as brain temperature susceptibility to damage in such cases needs to be managed effectively.

Materials and methods

During intrauterine life, the fetus generates heat through its metabolic processes. Power et al. conducted a study measuring fetal heat production in sheep. They found that fetal sheep produced approximately 3.3 watts per kilogram of fetal tissue, equivalent to 47 calories per minute, which is roughly twice the heat production per unit of body weight compared to adults.

Traditionally, fetal heat production has been estimated by measuring oxygen consumption. Asakura et al. directly measured oxygen consumption in fetal lambs by oxygenating them after umbilical cord occlusion. Fetal oxygen consumption was recorded at 6.7 ml per kilogram per minute, which is 1.5 times higher than that of adult lambs. Other researchers have employed various methods to measure fetal oxygen consumption, yielding values ranging between 5 and 8 ml per kilogram per minute. These studies suggest that the basal metabolic rate of the fetus surpasses that of an adult, resulting in significant heat production. Additionally, it's reported that the placenta and uterine wall contribute approximately 2.1 watts per kilogram of tissue to this heat production, consequently raising fetal temperature.

Body temperature is determined by the equilibrium between heat production and heat loss. When heat production increases, body temperature rises, and vice versa. Given that fetal temperature is naturally higher than maternal temperature, it's physiological for the heat generated by the fetus to be transferred to the mother. Gilbert et al. observed in sheep that heat passes readily across the placenta compared to transfer across the fetal skin. They noted that 85% of the heat produced by the fetal lamb

is transferred to the mother through the umbilical circulation, while the remaining 15% is dissipated through the fetal skin to the amnion, then through the uterine wall to the maternal abdomen.

As long as fetal heat production and loss are balanced appropriately, the temperature difference between the fetus and the mother remains constant (referred to as the "heat clump"), ensuring the appropriate amount of heat is transferred to the mother. However, if heat transfer is disrupted for any reason, fetal temperature may increase. Given that the majority of fetal heat is dissipated via umbilical blood flow, we discuss cases involving alterations in umbilical blood flow, which are common clinical scenarios during pregnancy and labor. An animal study demonstrated that partial occlusion of the umbilical cord elevated the body temperature of fetal baboons. Similarly, the body temperature of fetal sheep rose rapidly following complete occlusion of umbilical blood flow. Using tele-thermography, it was observed that the skin temperature of human newborns shortly after birth was relatively higher when the umbilical cord was coiled. This suggests that fetal temperatures rapidly change in response to disruptions in umbilical blood flow, as heat accumulates within the fetus.

One of the most severe umbilical cord problems for fetal viability is prolapse, which can disrupt blood flow and lead to acute hypoxic-ischemic brain damage. However, even in such critical clinical situations, the significance of fetal temperature in humans is not well understood. It is probable that, similar to animal models, human fetal temperature rapidly increases after occlusion of umbilical cord blood flow, as heat cannot dissipate effectively via the umbilical circulation.

The impact of maternal fever on fetal temperature warrants consideration. When a pregnant woman develops a fever, the temperature of the uterus, amnion, and blood increases, leading to reduced heat loss from the fetus to the mother and the accumulation of heat within the fetus, akin to fetal hyperthermia. Experiments conducted on fetal lambs have revealed that both umbilical and uterine arterial blood flow decrease when the mother experiences hyperthermia. Specifically, a maternal temperature increase of 2.5℃has been shown to significantly reduce umbilical cord blood flow.

When a pregnant woman develops a fever, increased blood flow to the skin facilitates the dissipation of heat. However, this adaptation comes at a cost, as blood flow to vital organs such as the kidneys, intestines, and uterus decreases. Consequently, maternal hyperthermia may diminish uterine, uteroplacental, and umbilical blood flow, potentially leading to fetal hypoxia or acidosis. These findings underscore the serious fetal consequences associated with hyperthermia during pregnancy.

Results and discussions

Upon birth, neonates experience rapid heat loss due to the transition from the warm intrauterine environment to the relatively cold external environment. Evaporative heat loss becomes significant, leading to a rapid drop in neonatal temperature. Consequently, increased fetal heat production becomes crucial for the neonate's survival. The thermogenic response initiates within minutes of birth and persists for several hours. For instance, in humans, oxygen consumption and heat production of neonates increase two to threefold during cold stress at birth.

Two modes of heat production have been identified: (1) Basic heat production resulting from increased cellular metabolic activity, and (2) Additional heat production when required, such as during cold stress. Extra heat production includes nonshivering and shivering thermogenesis, with the latter involving heat generation through shivering skeletal muscles. However, since neonatal muscles are relatively immature for heat production, shivering thermogenesis is considered insignificant. The crucial role of nonshivering thermogenesis (NST) at birth has been well recognized, with heat being produced in brown adipose tissue.

Brown adipose tissue differs morphologically and metabolically from ordinary white adipose tissue, containing numerous mitochondria, abundant fat vacuoles, a rich sympathetic innervation, and a plentiful blood supply. Within the mitochondria of brown adipose tissue, ATP synthesis is uncoupled from the oxidative process by a protein situated in the inner mitochondrial membrane, known as an "uncoupling protein." This uncoupling leads to heat production as a final product, accompanied by an increase in oxygen consumption and elevation of free fatty acids in the serum due to the lipolysis of brown adipose tissue.

In species such as lambs, rabbits, and rats, significant NST commences in brown adipose tissue shortly after birth. Although not as pronounced, a similar response is observed in human newborns. Brown adipose tissue accounts for only 1.4% of the body mass of human newborns weighing over 2,000 grams. It is prominently located in nuchal subcutaneous tissue, the intrascapular region, the mediastinum, surrounding the spinal cord, and around the kidneys. Thus, the initiation of NST in brown adipose tissue contributes to the elevation of core body temperature in neonates.

Conclusion

In this review, the physiology of fetal and neonatal thermoregulation has been examined. While the data primarily originates from animal studies, there is a clear need for research involving human subjects to enhance the clinical care of fetuses and neonates. While we have gained insights into the thermoregulatory mechanisms of fetuses and neonates, the clinical management of their thermoregulation remains inadequately established beyond the standard thermal care of neonates. For instance, in cases of severely distressed fetuses or neonates due to umbilical cord occlusion in utero, there is currently no well-defined treatment to prevent brain damage. Despite the fact that body temperature may rise while brain temperature remains normal, the body temperature promptly drops after delivery, and as severely distressed neonates are hypoxic, sufficient oxygen and heat are crucial to elevate temperature via nonshivering thermogenesis. Questions such as whether to cool the brain to prevent damage and when to initiate brain cooling remain unanswered in clinical practice.

Brown adipose tissue can produce adequate heat for neonates at birth through uncoupling protein. Recent discoveries of various subtypes of uncoupling protein in multiple organs suggest that the role of uncoupling protein extends beyond thermoregulation to include energy expenditure, as observed in pregnant women. Given that uncoupling proteins are found across various species, including mammals, birds, insects, and plants, further investigation into these proteins may lead to a deeper understanding of fetal and neonatal physiology.

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