Effects of body temperature maintenance on glucose, insulin, and corticosterone responses to acute hypoxia in the neonatal rat

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Guenther MA, Bruder ED, Raff H. Effects of body temperature maintenance on glucose, insulin, and corticosterone responses to acute hypoxia in the neonatal rat. Am J Physiol Regul Integr Comp Physiol 302: R627–R633, 2012. First published December 7, 2011; doi:10.1152/ajpregu.00503.2011.—One of the biggest challenges of premature birth is acute hypoxia. Hypothermia during acute hypoxic periods may be beneficial. We hypothesized that prevention of hypothermia during neonatal hypoxia disrupts glucose homeostasis and places additional metabolic challenges on the neonate. Pups at postnatal day 2 (PD2) were exposed to 8% O2 for 3 h, during which they were allowed to either spontaneously cool or were kept isothermic. There was also a time control group that was subjected to normothermia and kept isothermic. Plasma glucose, insulin, C-peptide, corticosterone, and catecholamines were measured from samples collected at baseline, 1 h, 2 h, and 3 h. In postnatal day 2 (PD2) rats, hypoxia alone resulted in no change in plasma glucose by 1 h, an increase by 2 h, and a subsequent decrease below baseline values by 3 h. Hypoxia with isothermia in PD2 rats elicited a large increase in plasma insulin at 1 h. In PD8 rats, hypoxia with isothermia resulted in an initial increase in plasma glucose, but by 3 h, glucose had decreased significantly to below baseline levels. Hypoxia with and without isothermia elicited an increase in plasma corticosterone at both ages and an increase in plasma epinephrine in PD8 rats. We conclude that the insulin response to hypoxia in PD8 rats is associated with an increase in glucose similar to an adult; however, insulin responses to hypoxia in PD2 rats were driven by something other than glucose. Prevention of hypothermia during hypoxia further disrupts glucose homeostasis and increases metabolic challenges.

isothermia; newborn; pancreas; oxygen; C-peptide; catecholamines

ACUTE HYPOXIA IS A COMMON neonatal stressor, particularly in babies born prematurely (15, 25–27). Acute hypoxia imposes significant metabolic and neurological challenges in neonates and can harm the developing brain (12). Treatment of hypoxia often requires the use of mechanical ventilation, supplemental oxygen, and other therapies (30, 34, 45, 46). Acute hypoxia in the neonate can also lead to hypothermia, which may alter metabolism and allow a decrease in oxygen consumption as a protective mechanism (9, 16, 29, 50). To our knowledge, there are no specific guidelines regarding the control of body temperature (Tb) during episodes of acute hypoxia in human neonates. However, it is recommended that the core body temperature of a human neonate be maintained at about 37°C (10, 23, 24). Interestingly, half of full-term neonates have body temperatures below the normal range (23). The consensus seems to be that prevention of hypothermia for preterm infants and nonasphyxiated term infants is warranted (10, 23, 24, 48).

Despite this, maintaining isothermia during hypoxia may place additional metabolic demands on the neonate and result in neurological injury.

We have characterized the spontaneous decrease in Tb that occurs during acute hypoxia in the neonatal rat (6, 7). This “hypoxic thermal response” is thought to protect the neonate from metabolic and neurological morbidity (35, 43). We have also previously demonstrated that preventing hypothermia increased the corticosterone response to acute hypoxia, the archetypal index of an augmented stress response (6, 7).

The current study evaluated plasma glucose, insulin, C-peptide, corticosterone, and catecholamine responses at 1, 2, and 3 h of acute hypoxia in neonatal rats without and with control of Tb using external heat. We hypothesized that maintenance of Tb during hypoxia would disrupt glucose homeostasis and be an additional metabolic challenge in the neonatal rat.

METHODS

Animal treatment and experimental protocol. The Aurora Health Care Institutional Animal Care and Use Committee approved the animal protocol. Timed-pregnant Sprague-Dawley rats at gestational day 15 (n = 51) or 18 (n = 51) were obtained from Harlan Sprague Dawley (Indianapolis, IN) and were maintained on a standard diet and water ad libitum in a controlled environment (0600–1800 lights on). Pups were studied at postnatal days 2 and 8 (PD2 and 8). Although it is difficult to compare the timing of maturation of the newborn rat to the neonatal human, these ages were chosen as a time span that approximates the perinatal period of the human, particularly as it relates to the development of the central nervous system (2, 39, 47). Furthermore, we have previously shown that the period of PD2 to PD8 is the transitional time from neonatal to adult hypothalamus-pituitary-adrenals (HPA) axis dynamics for the response to hypoxia (6, 7). Prior to experimentation, litters were separated from the dams, and pups from each litter were randomly divided into four equal sets (12–20 rats/set; mixed sexes), and placed in an environmental chamber. Each group of rats was kept separate during the experiment, with each group occupying a 6 × 12 in. area in the chamber. Rats were allowed to nest and huddle on an adequate amount of bedding. Room air (21% O2) was supplied to the chamber at a rate of 8 l/min, and Tb was recorded in one sentinel pup maintained with each group using RET-3-Iso rectal probes and a BAT-12 digital thermometer connected to a SBT-5 switchbox (Physitemp Instruments, Clifton, NJ). During the initial 30-min prehypoxic period, Tb of sentinel rats was maintained using servo-controlled heat by adjusting the setting on a standard heating pad (Moor Medical LLC, Farmington, CT) placed underneath the bedding. On the basis of previous reports, our target Tb was maintained around the normal of 34°C to mimic the body temperature of the pups in the nest (1, 37, 44). The thermonuclear zone for neonatal rats is ~34–36°C (1, 4, 44). It is obviously not feasible to warm our animal room to 35°C, so we used the heating pad to keep the neonates at the optimal core body temperature measured rectally. Following the prehypoxic period, inflow O2 concentration was decreased to 8% for 3 h for both hypoxia groups. One group of hypoxic

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pups was allowed to spontaneously cool (Hypoxia group). In the other group, \( T_B \) was maintained using servo-controlled heat (Hypoxia+heat group), as described previously (6). Normoxic (time control) rats were exposed to 21% \( O_2 \) with maintenance of \( T_B \) by adjusting the setting on a heating pad (Normoxia+heat group). The rats used to obtain the catecholamine data were studied previously and did not receive servo-controlled heat during the 30-min prehypoxic period. Otherwise, the protocol was identical to that described above.

**Sample collection.** At baseline, 1, 2, and 3 h of 8% (Hypoxia group) or 21% \( O_2 \) (Normoxic time control group), 2 or 3 rats from each group were removed from the chamber and killed, and trunk blood was pooled in tubes containing EDTA.

**Hormone and glucose assays.** Plasma insulin (Crystal Chem, Downers Grove, IL) and proinsulin (Mercodia, Winston Salem, NC) were measured by ELISA. The intra-assay variability and the inter-assay variability were <10% for the insulin assay, and the sensitivity was 0.1 ng/ml. There was 30% cross reactivity of proinsulin in the insulin assay. For the proinsulin assay, intra-assay variability was 7%, the inter-assay variability was 8%, and the sensitivity was 0.03 ng/ml. Plasma glucose was measured spectrophotometrically using the glucose oxidase method (Pointe Scientific, Canton, MI). The intra-assay variability was 0.6%, the interassay variability was 1.9%, and the sensitivity was 5 mg/dl. Plasma C-peptide (Millipore, Billerica, MA) and corticosterone (MP Biomedicals, Solon, OH) were measured by radioimmunooassay. C-peptide interassay variability was 6.5–7.5%, and the sensitivity was 0.08 ng/ml. For the corticosterone assay, the intra-assay variability was 4.4–10.3%, and the interassay variability was 6.5–7.2%, while the sensitivity was 10 ng/ml.

Plasma catecholamine concentrations were measured by a refinement of a tissue method used previously (5). Samples for catecholamine analysis were extracted with acid-washed alumina containing 3,4-dihydroxybenzylamine as an internal standard. Every group of samples was extracted and analyzed with standards and quality control pools. Epinephrine and norepinephrine were measured by HPLC and electrochemical detection using an isocratic pump (Hitachi L-7000, San Jose, CA), a rheodyne 7125 manual injector (Supelco, Bellefonte, PA), a Chromat-integrator (Hitachi D-2500), a Supelcosil LC18 Column (Supelco), and an electrochemical detector (Bioanalytical Systems LC-4B, West Lafayette, IN). The mobile phase was 25 mM citric acid, 25 mM sodium phosphate dibasic anhydrous, 1 mM disodium EDTA, and 40–45 mg/l sodium octyl sulfate at a flow rate of 0.75 ml/min at 25°C. The electrochemical detector settings were 650 mV applied potential, 1 nA sensitivity, and 0.4 offset. Intra-assay variability was 5.5% and 7.9% for norepinephrine and epinephrine, respectively (\( n = 7 \)). Interassay variability was 7.4% and 9.3% for norepinephrine and epinephrine, respectively (\( n = 34 \)). The recoveries of 50 pg standard added to plasma samples were 79% for norepinephrine and 68% for epinephrine. For the catecholamine data, \( n = 8–18 \) measurements per time point.

**Statistical analyses.** Plasma hormone and glucose data were analyzed by two-way ANOVA, and body temperature measurements were analyzed by two-way ANOVA for repeated measures (\( P < 0.05 \) considered significant). All the data were expressed as means ± SE and were normally distributed. All post hoc analyses were performed by Student-Newman-Keuls method for multiple comparisons (Sigmastat 2.03).

**RESULTS**

Four sets of pups (\( n = 12–20 \) pups/set) were studied on each experimental day. Baseline plasma glucose, insulin, C-peptide, and corticosterone measurements are shown in Table 1. Because the prehypoxic treatment was identical for all of the rats used to obtain data for glucose, insulin, C-peptide, and corticosterone measurements, we used pups from all groups to generate baseline samples prior to application of the treatment. Once we collected the baseline samples, one of the three treatments was randomly assigned to each group. Plasma glucose was higher in the PD8 rats compared with the PD2 rats at baseline, though plasma insulin was roughly the same. Both plasma C-peptide and corticosterone were higher at baseline in the PD2 rat compared with the PD8 rat.

Body temperature (\( T_B \)) data for PD2 and PD8 rats are shown in Fig. 1. Body temperatures (\( T_B \)) were recorded from four different sentinel pups per experiment (one sentinel/set). At both ages, \( T_B \) was successfully maintained (~34°C) during

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**Table 1. Baseline plasma glucose, insulin, C-peptide, and corticosterone concentrations in PD2 and PD8 pups**

<table>
<thead>
<tr>
<th></th>
<th>PD2</th>
<th>PD8</th>
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<tbody>
<tr>
<td>Glucose, mg/dl</td>
<td>84 ± 2</td>
<td>130 ± 2*</td>
</tr>
<tr>
<td>Insulin, ng/ml</td>
<td>0.34 ± 0.05</td>
<td>0.37 ± 0.04</td>
</tr>
<tr>
<td>C-Peptide, ng/ml</td>
<td>4.89 ± 0.33</td>
<td>2.09 ± 0.13*</td>
</tr>
<tr>
<td>Corticosterone, ng/ml</td>
<td>32 ± 5</td>
<td>13 ± 2*</td>
</tr>
</tbody>
</table>

Values are expressed as means ± SE; \( n = 24–28 \) measurements per analyte at each age. *Significantly different from postnatal day 2 (PD2) with \( P < 0.001 \).
normoxia or hypoxia with servo-controlled heat throughout the 3-h experimental period, regardless of inspired oxygen concentration (Normoxia+heat and Hypoxia+heat groups; \( P > 0.05 \)). Minimal heat (heating pad on low) was required to maintain \( T_B \) in pups from the Normoxia+heat group, while more heat (heating pad on medium/high) was needed to maintain \( T_B \) in pups from the Hypoxia+heat group. When servo-controlled heat was not used during hypoxia, \( T_B \) had decreased significantly by 30 min of exposure (both ages; \( P < 0.001 \)). PD2 and PD8 pups exposed to hypoxia alone had final \( T_B \) values of 23.2 ± 0.6 and 24.6 ± 0.3°C, respectively (\( P < 0.001 \) compared with normoxia+heat and hypoxia+heat groups).

Figure 2 shows plasma glucose, insulin, and C-peptide concentrations in PD2 pups. Plasma glucose was decreased at 1 and 2 h in the Normoxia+heat group compared with baseline (\( P < 0.02 \)). By 3 h, glucose was not different from baseline in the Normoxia+heat group (\( P > 0.05 \)). Hypoxia alone resulted in increased plasma glucose at 2 h (\( P = 0.041 \)); however, glucose concentrations at 3 h were lower than baseline (\( P = 0.028 \)). Maintaining \( T_B \) during hypoxia (Hypoxia+heat) resulted in a decrease in plasma glucose at 3 h compared with baseline (\( P = 0.031 \)). Plasma insulin was increased at 1 h in PD2 pups in the Normoxia+heat group (\( P < 0.001 \)). Hypoxia resulted in an increase in plasma insulin at 1 h (\( P = 0.002 \)), and insulin further increased at 3 h (\( P < 0.001 \)). A large increase in plasma insulin after 1 h (\( P < 0.001 \)) was observed in the Hypoxia+heat group, but insulin levels had declined at 2 h (\( P = 0.011 \)) and returned to baseline by 3 h (\( P > 0.05 \)). Plasma C-peptide did not change in any of the three treatment groups during the first 2 h (\( P > 0.05 \)); however, at the 3-h time point, C-peptide had increased in pups in the Hypoxia group (\( P = 0.024 \)) and decreased in Normoxia+heat group (\( P = 0.001 \); compared with baseline).

Plasma glucose, insulin, and C-peptide data for PD8 pups are shown in Fig. 3. Plasma glucose was decreased at 1 h in the Normoxia+heat group (\( P = 0.006 \)) and remained below baseline at 2 (\( P = 0.003 \)) and 3 h (\( P = 0.008 \)). Hypoxic pups had an increase in plasma glucose concentrations at 1 (\( P = 0.014 \)), 2 (\( P < 0.001 \)), and 3 h (\( P = 0.042 \)). The Hypoxia+heat group had increased plasma glucose at 1 h (\( P = 0.004 \)), but by 3 h, glucose concentrations decreased markedly to below baseline values (\( P < 0.001 \)). Plasma insulin was increased after 2 h in pups from the Normoxia+heat group (\( P = 0.001 \)) but returned to baseline values by 3 h (\( P > 0.05 \)). Plasma insulin was increased at 2 and 3 h in pups from the Hypoxia group (\( P < 0.001 \)). Plasma insulin was unchanged in the Hypoxia+heat group (\( P > 0.05 \)). Plasma C-peptide decreased from baseline after 3 h during normoxia and heat (\( P = 0.018 \)). Plasma C-peptide increased at 2 h in the Hypoxia group (\( P < 0.001 \)), but by 3 h, C-peptide levels had decreased to below baseline values (\( P = 0.044 \)). C-peptide decreased to levels below those of baseline at 3 h in the Hypoxia+heat group (\( P < 0.001 \)).

Plasma corticosterone for PD2 and PD8 pups is shown in Fig. 4 (note log scale). Please note that the 3-h time point data have been published previously (6), but they are shown here for reference to the current data. Plasma corticosterone levels did not change in PD2 pups from the Normoxia+heat group (\( P > 0.05 \)). Plasma corticosterone was increased in Hypoxia and Hypoxia+heat PD2 groups at 1 and 2 h (\( P < 0.001 \)). In PD8 pups, plasma corticosterone increased at 1 h in the Normoxia+heat group (\( P = 0.040 \)), but it had returned to baseline by 2 h (\( P > 0.05 \)). For PD8 pups, both Hypoxia and Hypoxia+heat groups elicited an increase in plasma corticosterone at 1–3 h (\( P < 0.001 \)). At both PD2 and PD8, plasma corticosterone was higher in the Hypoxia+heat
Hypoxia, and Hypoxia+heat groups, respectively. There were no significant differences between any of the groups ($P > 0.05$). Plasma proinsulin in the PD8 rat was $0.02 \pm 0.005$, $0.04 \pm 0.02$, and $0.01 \pm 0.002$ ng/ml after 1 h in the Normoxia+heat, Hypoxia, or Hypoxia+heat groups, respectively.

Plasma catecholamines were measured in a separate set of samples (see METHODS). Baseline norepinephrine concentrations were significantly lower in PD2 rats (1,250 ± 96 pg/ml) compared with PD8 rats (1,713 ± 118 pg/ml). Plasma norepinephrine was not significantly affected by acute hypoxia with spontaneous hypothermia (1,128 ± 135 pg/ml) or with maintenance of isothermia (1,080 ± 159 pg/ml) in PD2 rats. There was no effect of hypoxia with hypothermia on plasma norepinephrine in PD8 rats (1,565 ± 144 pg/ml), while maintenance of isothermia resulted in an increase in plasma norepinephrine at this age (2,284 ± 234 pg/ml). Baseline epinephrine concentrations were also significantly lower in PD2 rats (782 ± 97 pg/ml) compared with PD8 rats (3,108 ± 214 pg/ml). Plasma epinephrine was not affected by either hypoxia with or without heat in PD2 rats. Acute hypoxia with hypothermia resulted in a significant epinephrine response in PD8 rats (5,006 ± 520 pg/ml), and a similar response was observed when isothermia was maintained (5,640 ± 887 pg/ml).

**DISCUSSION**

We addressed the hypothesis that maintenance of $T_B$ during hypoxia would disrupt glucose homeostasis and be an additional metabolic challenge in the neonatal rat. Maintenance of $T_B$ during hypoxia (Hypoxia+heat group) elicited a large, initial increase in insulin in PD2 rats, despite no change in plasma glucose. In PD8 rats, plasma glucose increased initially at 1 h followed by a large decrease by 3 h in the Hypoxia+heat group, with no changes in insulin or C-peptide. Both hypoxia with and without heat elicited an increase in plasma corticosterone at both ages. In PD8 pups, both hypoxia with and without heat elicited an increase in plasma epinephrine, and hypoxia with heat elicited an increase in plasma norepinephrine. The insulin and glucose data confirm our hypothesis that maintenance of body temperature significantly alters the control of glucose during neonatal hypoxia despite similar increases in the plasma levels of counterregulatory hormones (corticosterone and epinephrine).

**Body temperature.** The spontaneous reduction in $T_B$ in response to acute hypoxia is thought to be a protective mechanism that allows a beneficial decrease in metabolic rate in the face of a decreased $O_2$ supply (9, 16, 29, 50). We have shown previously that prevention of this spontaneous decrease in $T_B$ with the use of servo-controlled external heat during 3 h of hypoxia augmented corticosterone responses in the PD2 and PD8 rat (6). To our knowledge, there are no specific guidelines that address $T_B$ management during a hypoxic episode in a human neonate. The decrease in $T_B$ that we observed may allow a decrease in oxygen consumption at the cellular level to match the decreased oxygen supply (28, 29). Others have shown that hypothermia may be used to help improve the outcome of infants with moderate or severe hypoxic-ischemic encephalopathy (20, 32, 41).

**Insulin.** An insulin response is typically mediated by an increase in extracellular glucose, but PD2 rats did not appear to
fetal and neonatal hyperinsulinemia has been associated with glucose uptake in tissue. Hyperinsulinemia has been shown to occur during perinatal asphyxia in humans (12). In addition, SNS may signal the islets of the pancreas. Sympathetic nerve fibers have extensive innervation of pancreatic islet cells during the neonatal period (8). As a result of a physiological challenge like hypoxia, the SNS may signal the β-cells to produce insulin to maximize glucose uptake in tissue. Hyperinsulinemia has been shown to occur during perinatal asphyxia in humans (12). In addition, fetal and neonatal hyperinsulinemia has been associated with adult-onset obesity, insulin resistance, hypertension, and vascular disease in later life (3, 18, 19, 42).

We observed a different insulin response when $T_B$ was maintained during hypoxia in PD2 rats. After 1 h, insulin nearly quadrupled, but by 3 h, it had returned to the baseline level. We previously suggested that aggressive maintenance of $T_B$ during hypoxia was harmful because it may expose the neonate to high glucocorticoid levels and metabolic challenges (6). The increases in glucocorticoids likely affected glucose homeostasis by altering insulin sensitivity and pancreatic hormone levels. Interestingly, the difference in plasma corticosterone between pups exposed to hypoxia vs. hypoxia and heat previously observed at 3 h in our previous study (6) was not observed at either the 1- or 2-h time points.

While the insulin response in PD2 pups may have been driven by the SNS, the insulin response in PD8 rats was associated with an increase in plasma glucose similar to an adult. We have previously shown that the HPA axis response to hypoxia in PD8 rats is similar to that of adults (6, 7). In the present study, hypoxia alone elicited an increase in plasma glucose, which may have resulted from the increase in corticosterone and insulin resistance. In turn, the increase in glucose could have increased plasma insulin, because we speculate that the β-cells of PD8 rats respond directly to increased concentrations of glucose as in the adult rat (6, 7).

When $T_B$ was maintained during hypoxia in PD8 rats, there was no insulin response despite changes in plasma glucose. The PD8 rats were able to maintain relatively high levels of plasma glucose until the 3-h time point, at which point plasma glucose plummeted to well below baseline values. It may be that external heat increased the metabolic rate, so glucose was consumed at a much higher rate. Despite the fact that elevated levels of corticosterone normally promote hepatic gluconeogenesis, PD8 pups still became hypoglycemic, which may have been the result of increased glucose consumption. Hypoglycemia is obviously a severe threat to the neonate, and others have shown that hypoglycemia as a result of hypoxia leads to long-term neurological dysfunction in humans (12, 13). We have previously suggested that it may be beneficial to let the neonate spontaneously cool during acute hypoxic episodes (6). The present study supported this suggestion, because maintaining $T_B$ during hypoxia elicited a dramatic decrease in plasma glucose at 3 h compared with PD8 pups that were allowed to spontaneously cool.

C-peptide. We observed a dissociation between plasma insulin and plasma C-peptide concentrations at some time points. Plasma insulin and C-peptide were used as indices of islet cell function vs. the metabolic clearance of insulin. Of particular interest was the burst of plasma insulin observed at 1 h in the Hypoxia+heat group in PD2 rats with no corresponding change in plasma C-peptide. We also observed this dissociation in PD8 rats at 3 h of hypoxia alone. Others have shown a dissociation of insulin and C-peptide in diabetic humans treated with a drug that promotes insulin release from the pancreas, raising the possibility that the increase in plasma insulin that we measured came from a source other than the pancreas, such as the liver (40). Another possibility we considered was that proinsulin increased and cross-reacted in the
insulin assay. However, we demonstrated that the large increase in plasma insulin after 1 h of hypoxia was not due to the release of proinsulin into the blood.

There were also differences between the magnitudes of the concentrations of plasma insulin and plasma C-peptide at baseline in both PD2 and PD8 pups. Baseline C-peptide was roughly 14 times higher than insulin in the PD2 rat, but only 6 times as high in the PD8 rat, suggesting that the PD2 rats are producing more insulin from the pancreas and/or that C-peptide is being metabolized at a slower rate than in the PD8 rats. Others have shown higher plasma C-peptide concentrations relative to plasma insulin in PD6 rats with ghrelin administration (33). It is well known that the metabolic clearance rate of insulin is significantly greater than that of C-peptide in the rat (21), indicating a possible explanation for the dissociation of plasma insulin and C-peptide in our current study.

Catecholamines. Neither hypoxia with nor without heat elicited a catecholamine response in the PD2 rats. The adrenal epinephrine release in the PD8 pups was likely due to neurogenic activation of the adrenal medulla (14). On the other hand, only hypoxia with heat induced an increase in norepinephrine, indicating an increase in SNS activity when body temperature is maintained. We suggest that the peripheral norepinephrine response induced by maintaining body temperature in PD8 rats may have acted centrally to further activate the HPA axis (22, 49).

Cortisol. The corticosterone response to hypoxia with or without heat in the PD8 rat was similar to that of the PD2 rat, although the magnitude was smaller at PD8. As we have shown in a previous study, plasma corticosterone levels after 3 h of hypoxia with heat were higher than those after hypoxia alone (6). This demonstrates an additional harm of maintaining $T_B$ during hypoxia. Overexposure of a developing organism to glucocorticoids has been linked to permanent changes in glucose and insulin metabolism, which may result in diabetes or obesity later on in life (36). Maintaining $T_B$ during hypoxia also had a negative impact on glucose homeostasis. In PD8 rats, the addition of external heat may have increased glucose consumption, and, as a result, caused severe hypoglycemia after 3 h.

**Perspectives and Significance**

Hypoglycemia should be avoided in neonates, as it can lead to poor neurological development (12, 13). In the PD2 rats, there was a significant decrease in plasma insulin from 1 to 3 h as a result of hypoxia with heat. This decrease in insulin may not be beneficial to the animal, as it may lead to a decrease in glucose uptake by tissue. This is counteracting the mechanism we proposed, by which the SNS stimulates insulin release from the ß-cells in the pancreas to maximize glucose uptake in vital tissues during the hypoxic period. It has been shown that maintaining body temperature during hypoxia in neonatal kits increased cardiac output and also lowered systemic vascular resistance compared with animals that were allowed to cool during hypoxia (38). Maintenance of body temperature during hypoxia may pose a serious threat to the neonate. It may be perceived as hyperthermia in a hypoxic period, during which the expected response is a decrease in body temperature (38).

We have provided evidence that maintaining $T_B$ during an acute hypoxic episode may put additional metabolic and physiological demands on a neonate. This was demonstrated by nonglucose-mediated hyperinsulinemia in PD2 rats and hypoglycemia in PD8 rats. Applying external heat may prevent the survival response in which the metabolism of the neonate is decreased to cope with the decrease in oxygen supply. Doing so may disrupt glucose homeostasis, thus resulting in short- or long-term harm to the neonate, which may include impaired neurological development. We hope that our studies in the neonatal rat will translate to appropriate studies in and guidelines for the control of $T_B$ in the hypoxic newborn.

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the authors.

**AUTHOR CONTRIBUTIONS**

Author contributions: M.A.G., E.D.B., and H.R. were responsible for conception and design of research; M.A.G., E.D.B., and H.R. performed the experiments; M.A.G., E.D.B., and H.R. analyzed the data; M.A.G., E.D.B., and H.R. interpreted the results of the experiments; M.A.G. and E.D.B. prepared the figures; M.A.G. and E.D.B. drafted the manuscript; M.A.G., E.D.B., and H.R. edited and revised the manuscript; M.A.G., E.D.B., and H.R. approved the final version of manuscript.

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