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Developmental changes in cold tolerance and ability to autoresuscitate from hypothermic respiratory arrest are not linked in rats and hamsters

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ABSTRACT

In adult mammals, severe hypothermia leads to respiratory and cardiac arrest, followed by death. Neonatal rats and hamsters can survive much lower body temperatures and, upon artificial rewarming, spontaneously recover from respiratory arrest (autoresuscitate), typically suffering no long-term effects. To determine developmental and species differences in cold tolerance (defined here as the temperature of respiratory arrest) and its relation to the ability to autoresuscitate, we cooled neonatal and juvenile Sprague-Dawley rats and Syrian hamsters until respiration ceased, followed by rewarming. Ventilation and heartbeat were continuously monitored. In rats, cold tolerance did not change throughout development, however the ability to autoresuscitate from hypothermic respiratory arrest did (lost between postnatal days, P, 14 and 20), suggesting that the mechanisms for maintaining breathing at low temperatures was retained throughout development while those initiating breathing on rewarming were altered. Hamsters, however, showed increased cold tolerance until P26–28 and were able to autoresuscitate into adulthood (provided the heart kept beating throughout respiratory arrest). Also, hamsters were more cold tolerant than rats. We saw no evidence of gasping to initiate breathing following respiratory arrest, contributing to the hypothesis that hypothermic respiratory arrest does not lead to anoxia.

1. Introduction

Hypothermia, a large unregulated decrease in body temperature (T_B), is a lethal condition for most mammals. Once a critically low T_B is reached, respiration ceases and is followed by cardiac arrest and ultimately death if the animal is not rewarmed. Early work by Adolph (1951) showed that most species of adult mammals, including rats, could not withstand body temperatures below 15–20 °C, although in some species (such as hamsters) adults were able to survive a T_B as low as 5 °C. He also found that neonates had an increased cold tolerance compared to their adult counterparts and both newborn rats and hamsters could tolerate temperatures as low as 1 °C (Adolph, 1951). Clearly, while adults lose cold tolerance, this is more profound in some species than others. Adolph (1948a,b) also found that neonates cooled until both respiration and cardiac arrest occurred, could spontaneously resume both rhythms on rewarming (autoresuscitation). Adults, however, could not; they required ventilatory assistance to resuscitate.

Several researchers have now documented the developmental decline in cold tolerance (defined as lower lethal temperature in such studies) (Adolph, 1948a,b, 1951; Adolph et al., 1961; Fairfield, 1948; Hill, 2000) and found that, in small mammals, it occurs predominantly between 10 and 20 days after birth. The time frame during which the ability to spontaneously recover from hypothermic respiratory arrest is lost, however, has not yet been documented. It has been shown that during lethal hypothermia, respiratory arrest occurs first and that the temperature threshold for this event is different from that for cardiac arrest (Hill, 2000). Thus, while the loss of the ability to autoresuscitate is undoubtedly related to the loss of cold tolerance, the relationship between these two is not clear. Thus in the present study we sought to determine the relationship between cold tolerance and the ability to autoresuscitate from hypothermic respiratory arrest as well as the developmental time frame during which changes in these variables occur in both rats and hamsters.

Many developmental changes in cardio-respiratory processes have now been observed in rats around postnatal days 10–12 (P10–12) including changes in chemosensitivity (Davis et al., 2006; Putnam et al., 2005; Wang and Richerson, 1999), responses to acute hypoxia (Liu et al., 2006), and neurochemical changes in brainstem nuclei involved in respiratory control (Wong-Riley and Liu, 2005, 2008). The second week of life appears to be a critical period for

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Table 1
Mean values of select variables during cooling and warming in rats.

	P0–6[a] (27)	P1 (4)	P16 (4)	P18–20 (4)
Mass (g)	10.8 ± 0.6	28.0 ± 1.5	34.3 ± 1.3	38.1 ± 1.9
f_R at 35 °C	93 ± 4	103 ± 13	161 ± 92	98 ± 21
f_H at 35 °C	349 ± 7	311 ± 29	373 ± 21	388 ± 54
Rate of cooling (°C/min)	0.45	0.37 ± 0.03*	0.29 ± 0.04	0.21 ± 0.03
Rate of re-warming (°C/min)	0.71	0.44 ± 0.0 (3)	0.41 (1)	-
T_B at respiratory arrest (°C)	10.7 ± 0.24	9.4 ± 2.0	9.9 ± 1.5	8.3 ± 1.7
f_H at respiratory arrest (beats/min)	41.2 ± 15.0	28.4 ± 11.5	23.9 ± 9.5	26.1 ± 7.3
T_B when breathing resumes (°C)	13.3 ± 0.4	13.5 ± 2.8 (3)	16.8 (1)	-
f_H when breathing resumes (beats/min)	27.4 ± 2.3	27.6 ± 10.8 (3)	29.0 ± 8.8 (1)	-
Survival (%)	100	75	25	0

Numbers in parenthesis = *n* values.
[a] Data for P0–6 rat pups from Tattersall and Milsom (2003).
* Significantly different from P16 and P18–20.

Table 2
Mean values of select variables during cooling and warming in hamsters.

	P2–3 (9)	P5–6 (9)	P8–9 (8)	P15–20 (3)	P26–28 (6)	P32–34 (7)	Adults (8)
Mass (g)	4.5 ± 0.2	7.8 ± 0.3	10.4 ± 0.5	16.9 ± 3.1	45.9 ± 2.6	52.5 ± 2.2	127.9 ± 6.3
f_R at 35 °C	53 ± 2	65 ± 6	58 ± 6	109 ± 28	206 ± 22	148 ± 35[a]	195 ± 20[a]
f_H at 35 °C	405 ± 15	420 ± 10	388 ± 12	474 ± 29	515 ± 3	259 ± 12[a]	337 ± 24[a]
Rate of cooling (°C/min)	0.49 ± 0.02	0.46 ± 0.02	0.47 ± 0.02	0.25 ± 0.04	0.22 ± 0.02	0.65 ± 0.05	0.35 ± 0.03
Rate of re-warming (°C/min)	0.66 ± 0.06	0.60 ± 0.04	0.57 ± 0.04	0.37 ± 0.03	0.42 ± 0.03	0.93 ± 0.11 (5)	0.53 ± 0.02 (5)
T_B at respiratory arrest (°C)	8.5 ± 0.07	4.9 ± 0.4	3.8 ± 0.3	3.5 ± 0.4	3.6 ± 0.4	8.9 ± 0.6	6.0 ± 0.7
f_H at respiratory arrest (beats/min)	38.5 ± 5.7	39.2 ± 5.0	25.7 ± 4.4	13.5 ± 0.6	18.6 ± 7.2	17.0 ± 1.2	19.3 ± 3.6
T_B when breathing resumes (°C)	20.3 ± 2.1	13.1 ± 2.1	10.8 ± 1.0	9.3 ± 0.6	11.0 ± 0.6	10.0 ± 0.6 (5)	7.7 ± 1.7 (5)
f_H when breathing resumes (beats/min)	78 ± 15	23 ± 3	24 ± 4	17 ± 2	18 ± 4	4 ± 1 (5)	16 ± 5 (5)
Survival (%)	100	100	100	100	100	71.4[b]	62.5[b]

Numbers in parenthesis = *n* values.
[a] Data recorded at 30 °C rather than 35 °C.
[b] Animals not surviving also went into cardiac arrest.

respiratory development (Wong-Riley and Liu, 2008). Accordingly, we hypothesized that the time course over which the switch from the neonatal to the adult phenotype for hypothermic respiratory arrest would occur in the rat would correspond with this time course. Furthermore, since it has been shown that hamsters are more cold tolerant than rats (Adolph, 1951), and that *in vitro* brainstem–spinal cord preparations from hamsters exhibit respiratory arrest and autoresuscitation at lower temperatures than

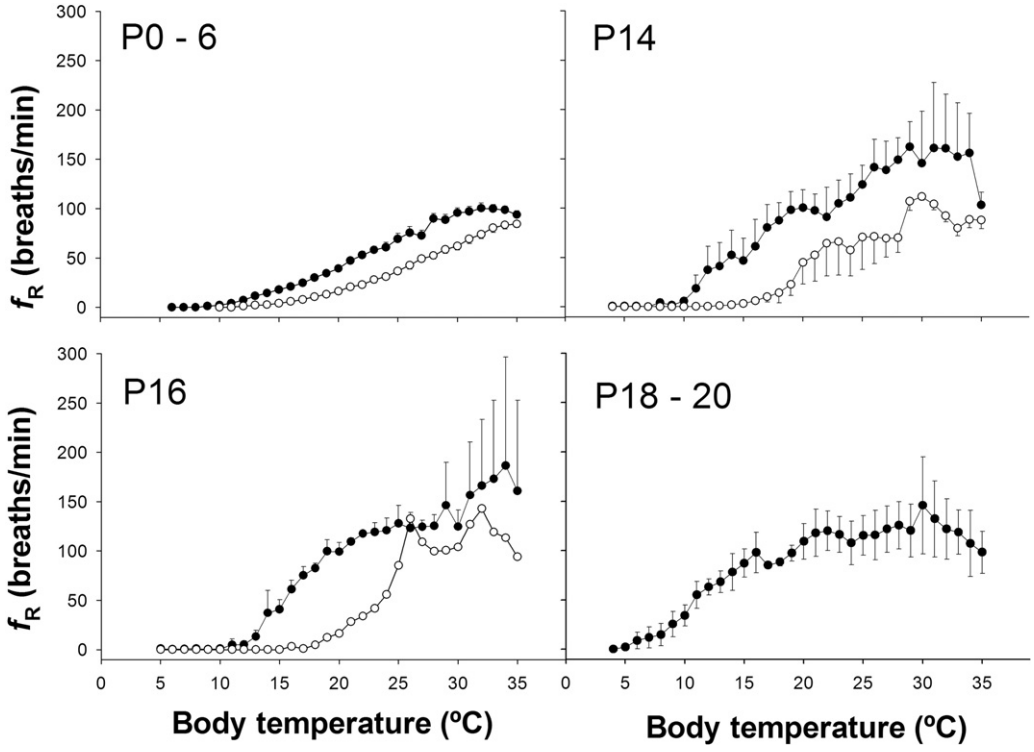

Fig. 1. Breathing frequency during transitional cooling (filled circles) and subsequent re-warming (open circles) in neonatal rats aged P0–6, P14, P16, and P18–20. Data are presented as absolute means ± SEM. Data for rats aged P0–6 were obtained from Tattersall and Milsom (2003).