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Development of Behavioral Responses to Thermal Challenges

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Abstract

Body temperature regulation involves the development of responses to cold and warm challenges. Matching our understanding of the development of body temperature regulation to warm challenges with that of cold challenges will enhance our understanding of the ontogeny of thermoregulation and reveal different adaptive specializations. Warm and cold thermoregulation are important processes, and they include direct thermal effects on offspring, as well as indirect effects on them, such as those imposed by thermally-associated alterations of maternal behavior. The present paper is a selective review of the existing literature and a report of some new empirical data, aimed at processes of mammalian development, especially those affecting behavior. We briefly discuss the development of body temperature regulation in rats and mice, and thermal aspects of maternal behavior with emphasis on responses to high temperatures. The new data extend previous analyses of individual and group responses in developing rodents to warm and cool ambient temperatures. This literature not only reveals a variety of adaptive specializations during development, but it points to the earlier appearance in young mammals of abilities to combat heat loss, relative to protections from hyperthermia. These relative developmental delays in compensatory defenses to heating appear to render young mammals especially vulnerable to environmental warming. We describe cascading consequences of warming – effects that illustrate interactions across levels of physiological, neural, and behavioral development.

Keywords

altricial rodents; elevated temperatures; development; social behavior; physiology; parent-offspring interactions

Body temperature regulation is a vital process that develops and changes over time with different mechanisms arising at different developmental periods. Assessing thermoregulation across different life stages can enhance our understanding about how these vital regulatory processes develop and change over time (e.g., infancy to adulthood), differ according to thermal challenge (e.g., cold, warm), and manifest in different social contexts (e.g., individual, group). The study of thermoregulation in adults is focused on how large animals

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expend heat to prevent overheating, which is in contrast to small infants where the emphasis on thermoregulation involves reducing loss of body heat to the environment, facilitating transfer from external sources of heat to their body, and then judiciously expending energy for heat production (Blumberg, 2001; Blumberg & Sokoloff, 1998). Consequently, most of the experimental literature on the development of body temperature regulation involves responses to cold challenges (Blumberg & Sokoloff, 1998; Harshaw, Blumberg, & Alberts, 2017; Satinoff, 1996), for this is the challenge typically faced by immature mammals. In contrast, the present paper is a selective review and discussion of data and knowledge about the ontogeny of regulatory responses to warm challenges, the less well known side of thermoregulation, but needed for general understanding and applicable to several basic concerns. We situate our presentation in different developmental contexts to provide a foundation for consideration of how individuals, families, and groups may respond to elevated temperatures.

For an appreciation of thermoregulation, we must understand the responses to conditions that would either lower or raise body temperature (Gordon, 2012; Tattersall et al., 2012). Adding knowledge of regulatory responses to warm challenges helps fulfill our basic understanding of thermoregulation. Clinically, there are numerous procedures, including incubators, heating pads, infrared radiation, and swaddling that raise the temperatures of infants, and therapeutic practice will be enhanced with greater understanding of developmental thermal responses. Furthermore, hyperthermia has been implicated in many cases of Sudden Infant Death Syndrome (SIDS; Nelson, Taylor, & Weatherall, 1989; Stanton, Scott, & Downham, 1980), possibly acting on developmental vulnerabilities in mechanisms by which infants “autoresuscitate” to overcome periods of apnea (Harper, Kinney, Fleming, & Thach, 2000; Kahraman & Thach, 2004). On ecological scales, current climatological projections of global warming indicate that there are increasingly more frequent and extreme spikes in ambient temperature (Walther et al., 2002), observations that have begun to raise questions and inspire inquiries into aspects of animal behavior and cognition that might be affected by climate change (see special issues Griffin, Tebbich, & Bugynar, 2017; Sih, 2013; Wong & Candolin, 2015).

Responses to High Temperatures

We begin with a brief overview of responses to thermal challenges, including morphological characteristics that affect warming and cooling of bodies and brains. Sweating, saliva spreading, gular sac extensions, and panting are examples of tactics used to reduce body temperature through evaporative cooling. Rodents are largely devoid of sweat glands, but they display copious salivation during heat stress (Hainsworth, 1967; Hainsworth & Stricker, 1970). The saliva is spread via grooming movements from the mouth to the body surface. Evaporative cooling occurs with removal of latent heat by liquid vaporization from the body surface (Tattersall et al., 2012).

Bodies gain heat by conduction when environmental surfaces are warmer than the animal's own surface temperature. In contrast, bodies lose heat by conduction when in or on a cooler surrounding. Conductance is lower in larger bodies; and conductance rate scales allometrically to body size (Schmidt-Nielsen, 1984). In addition, insulation and

vascularization can alter conduction. Morphological adaptations that affect conductance are considered ‘specialized surfaces’, and include bird bills, the ears of jack rabbits and elephants, hairless tails of rodents, and the naked legs of camels and ostriches. Physiologically, conductance can be altered by changing blood flow and by vasodilation and vasoconstriction. Behaviorally, animals can regulate conductance by selecting or creating microenvironments that afford body temperature regulation (Huey, 1991; Mathot & Dingemanse, 2015).

The brain is more autonomous than other organs, in the sense that it exerts control over its own temperature, blood flow, and metabolism (Kiyatkin, Kim, Wakabayashi, Baumann, & Shaham, 2015). Neuronal functions of all sorts, e.g., activity of single ion channels, transmitter release and reuptake, action potentials and integrative functions, are temperature dependent. Brain temperature is not uniform; various structures vary in temperature. The regulation of brain temperature is poorly understood and the questions and implications for function and cognition are just emerging. Nevertheless, the picture is already compelling: the brain’s function is susceptible to its own temperature. There exist numerous links between pathologies and altered brain temperatures (Kiyatkin et al., 2015). In addition, permeability of the blood-brain-barrier also appears to be temperature-sensitive (Kiyatkin & Sharma, 2009), so a full understanding of thermal-neural relations will likely involve an integrative perspective on brain-body interactions with temperature (Kiyatkin & Brown, 2004).

Developmental Considerations

Infants of endothermic species are typically limited in their capacities for body temperature regulation, relative to their adult counterparts. Smaller size is a major factor, because the correspondingly larger surface area:mass relation means that body heat is lost more rapidly from the infant’s smaller body (Schmidt-Nielsen, 1984). A consequence of the “surface law” is that small bodies also gain heat more rapidly from external sources. In the context of global warming, this factor should be kept in mind.

In addition to small size, however, a host of factors associated with altriciality (immaturity) render infants and juveniles thermally vulnerable. At birth, such mammals – which include the rodent species commonly used in lab research - lack insulative fur and subcutaneous fat (Figure 1). Autonomic control of vasodilation and vasoconstriction are limited. Shivering is absent until the middle of the first week (Arjamaa & Lagerspetz, 1979) or even until the third week of life (Taylor, 1960). Warming does not produce excessive salivation and saliva spreading until the middle of the second week of life (Pfister, 1990).

In the next sections, we chart some major life history stages of rodents, emphasizing the influence of elevated temperatures on development, including cognition and related processes.

Mammalian Mothers at Elevated Temperatures

A full appreciation of how elevated ambient temperatures can influence infant development must include effects that are transduced through the mother. Throughout gestation and most

of lactation, all the body-building and physiology-maintaining processes in the offspring are accomplished with resources supplied by the mother's metabolism. Generally, lactation is the most energy-demanding phase of the mammalian life cycle. Speakman and associates have advanced a Heat Dissipation Limit (HDL) theory, according to which the maximal capacity to dissipate body heat and thereby avoid hyperthermia sets the upper boundary on metabolism during lactation (Speakman & Król, 2010, 2011). The HDL theory is a more general, "ecological" framework that accounts for phylogenetic constraints on body size, morphology, and habits -- but we are limiting our discussion of it to the energetics of lactation.

For our purposes, the HDL theory focuses attention on the limits of the lactating female to dissipate the heat generated by her amplified metabolic activity. For example, lactating rodents may triple their daily food intake to fuel their lactational metabolism (Speakman & McQueenie, 1996). Contrary to some assumptions, this lactational hyperphagia is not bounded by the dam's ability to ingest or to process more food, or by the capacity of her lactational physiology. Instead, the upper boundary is the heat generated by her hypermetabolic state and her capacity to lose heat to the environment and thus avoid hyperthermia (Gamo et al., 2013; Simons et al., 2011; Speakman & McQueenie, 1996). Increased environmental temperature represents a greater challenge to an already tested physiological state.

The HDL theory predicts that lactating animals are prone to hyperthermia; there are supporting data. Decades prior to the formulation of the HDL theory, Leon and colleagues reported an extensive series of studies showing that a lactating Norway rats body temperature rises when in contact with a litter of pups (Adels & Leon, 1986; Leon, Crockery, & Smith, 1978). Throughout the three-week-long "cycle of maternal behavior" rat dams make regular visits to their nest, where they nurse, lick, and huddle with offspring. During the first week or so of the cycle, nest bouts are long, with dams and pups in contact for 80% of each day. But, after the second week, as the litter mass becomes larger and more thermogenic, maternal nest bouts become shorter and more numerous. With further development the bout frequency and bout duration decrease. The best correlate of the termination of a nest bout between mother and pups is a rise in the ventral temperature of the mother's body (Leon et al., 1978). Indeed, manipulations that hastened the rise of dam's ventral temperature shortened nest bouts and, conversely, manipulations that slowed warming of her ventrum increased the time she spent in contact with the litter (Leon et al., 1978). Interestingly, when these investigators manipulated pup temperature independently of that the dam, the mother's nest bout termination remained associated with her ventral temperature, and not the litter temperature, indicating that temperature regulation of the litter is a by-product of the mother's self-regulation, in concert with her nest building behavior and other factors that alter her body temperature.

There are numerous neuroendocrine correlates of maternal behavior in mammals (Rosenblatt, Mayer, & Giordano, 1988; Stolzenberg & Champagne, 2016). Among these, elevated lactational levels of progesterone have been posited to raise the mothers' thermal "set point", thus allowing for the typical, chronic elevation of maternal temperature (Adels & Leon, 1986). Elevated levels of corticosterone are necessary for potentiated maternal heat

production (Adels & Leon, 1986). Oxytocin, a neuropeptide especially prevalent in the maternal circulation and in the maternal brain, has thermogenic effects (Chaves, Tilelli, Brito, & Brito, 2013). Interestingly, all three of these hormones, as well as other endocrine correlates of lactation, are associated with alterations in mood, emotion, and related cognitive functioning (Brunton & Russell, 2008; Russell, Douglas, & Ingram, 2001). Thus, it is likely (though untested) that elevated ambient temperature will affect maternal behavior as well as its endocrine substrates—and that such variations in endocrine levels will affect cognitive processes in the mother, her behavior, and mother-offspring interactions. The same elevations in ambient temperature might directly or indirectly alter the developing social behavior and cognitive processes of the young. In Figure 2, we highlight some of the known and possible effects that elevated temperatures may have on maternal care and offspring.

In some studies, natural variation in maternal licking and grooming during the first week postpartum has been used to categorize mother rats (Champagne, Francis, Mar, & Meaney, 2003), as high licking and grooming (high-LG) mothers and low licking and grooming (low-LG) dams. Rat pups that receive high amounts of maternal licking and grooming (or in other studies, frequent nursing with an “arched back” posture) showed increased synaptogenesis in the hippocampus and enhanced learning and memory in adulthood, relative to pups that received low amounts of the same maternal behaviors (Liu, Diorio, Day, Francis, & Meaney, 2000). Similarly, pups that received higher contact-dependent maternal care also show decreased physiological and behavioral responses to stressors, and decreased anxiety (Caldji et al., 1998; Fish et al., 2004). Such alterations in hippocampal anatomy, along with effects on measures of learning and anxiety indicate that neuro-cognitive development is susceptible to variations in maternal behavior (Champagne, 2008; Weaver et al., 2004). Indeed, there is ample evidence from cross-fostering manipulations that these effects derive from mother-offspring behavioral interactions, and are not simply ‘genetically’ inherited (Champagne et al., 2003; Priebe et al., 2005). Thus, contextual factors such as temperature that can affect maternal behavior can be reflected in the developmental outcomes of the next generation.

Development of Behavioral Regulation by Individuals and Groups in Relation to Temperature

From birth to the eve of weaning (Postnatal Day 13), mother mice spent less than half of each day in a nest box with their young (Auclair, König, Ferrari, Perony, & Lindholm, 2014; König & Markl, 1987), leaving the litter to develop in the presence of 4–8 siblings, usually aggregated into a clump or huddle. It is well known that huddling enables adult endotherms to reduce heat loss and increase thermogenic efficiency. Surprising to many researchers, was the finding that immature rats and mice can derive similar benefits from huddling (Alberts, 2007; Blumberg & Sokoloff, 1998). Huddling conserves heat by reducing the exposed surface area of the bodies in the huddle, in effect producing a “single body” with a smaller surface:mass ratio than that of the bodies comprising the huddle.

One early finding is that rat pups interact during huddling in ways that actively regulate the surface area of the group in relation to the surrounding temperature (Alberts, 1978). Strikingly, huddles of rodent pups display group regulatory behavior at early postnatal ages

that have long been considered stages when the pups are essentially non-regulatory (Alberts & Schank, 2010; Blumberg & Sokoloff, 1998). Nevertheless, when they can interact as a group, the infants' regulatory capabilities can be readily seen.

A huddle of pups appears as a nearly constantly seething mass of bodies. But there is order to the turmoil. In a cool environment, pups probe and push into the depths of the group, often displacing littermates that appear on the surface. In a warm environment, pups actively move up to the surface, often covering or burying other pups. These temperature-dependent movements are analogous to convection currents and are termed "pup flow" within the huddle (Alberts, 1978).

In the present study, we measure on three, early postnatal days the individual- and group-level activities of mouse pups at cold and warm temperatures. Specifically, we examine the movements of individual, focal pups within a huddle, and then we examine the direction of pup flow at cold and warm temperatures.

Method

Subjects

We used litters of C57BL/6 mouse pups derived from stock originally purchased from Jackson Laboratory (Bar Harbor, Maine) and bred in the Indiana University's Animal Behavior Laboratory colony. Mothers delivered and reared pups in standard maternity tubs (27 cm × 17 cm × 13 cm high) with food and water available *ad libitum*. In the vivarium, there was a 14:10 h light/dark cycle (lights on at 0700h) and 22.0 ± 2 °C, and humidity 40% ambience.

Procedure

We used litters (6 pups/litter) on Postnatal day (P) 2, 4, or 8. Using a modified Latin square design such that randomly selected litters were manipulated at one, two or three ages (16 litters were tested at each age for a total of 35 litters). For each litter, we removed 6 pups from their home cage, selecting one pup to serve as the focal subject and marking it with a line of non-toxic paint across the crown of the head, the shoulder, and rump for behavioral scoring. We placed the pups in a conical enclosure with 30° sloping walls. The bottom diameter was standardized for each age, 22mm, 24mm, and 27.5mm for P2, P4, and P8, respectively. The enclosure was in a temperature-controlled chamber, maintained at 22°C (cool condition) or at 36°C (warm condition). We used an overhead Logitech digital camera to record the 1h trial. The video record provided a view of the pups on the upper surface of the clump of bodies contained in the funnel-like enclosure. We divided the circular field into quadrants to provide a metric of activity around the horizontal plane of the huddle. Immediately prior to recording the trial, we placed the focal pup and a styrofoam marker (about $0.7 \times 0.6 \times 1.5$ cm) of negligible weight (0.000018g) on top of the clump unobscured by littermates. This marker was used during video scoring to infer the predominant direction of pup flow, as described in the next section. A thermocouple thermometer (Omega HH806AW, St. Louis, MO) monitored the ambient air temperature.

Individual-level Behavior—The behavior of each focal pup was quantified, using the number of times at least a portion of all three stripes became visible to the camera above the huddle and the number of transitions made by the focal pup between the quadrants on the surface of the funnel for each focal pup. These measures yielded a score of ‘vertical flow’ and ‘horizontal flow’, respectively. The open-source program, CowLog (Hänninen and Pastell, 2009), was used for encoding and storage of these data.

Group-level Behavior—We measured the time that the marker was visible on the huddle surface. The marker served as a directional marker of pup flow. When the marker was on the litter surface for more than 50% of the time, then pup flow was predominantly downwards. When the marker was hidden for more than 50% of the time, pup flow was predominantly upward.

Statistical Analysis—To measure individual-level activity, we summed the frequency of appearances on the huddle surface (vertical flow) and the number of translocations across quadrants (horizontal flow) of each focal pup. To measure group-level activity, we computed the percentage of time the Styrofoam marker was hidden below the huddle surface. To examine the effects of Age (P2, P4, or P8) and Temperature (22°C, 36°C) on individual- and group-level responses, we ran separate two-way repeated measures ANOVA with Bonferroni adjusted pair-wise comparisons. We used Type III sums of squares to correct for unbalanced data (Shaw & Mitchell-Olds, 1993), and an alpha level of .05. We conducted all statistical analyses in R (R Core Team, 2015), using the ‘nlme’ (Pinheiro, Bates, DebRoy, Sarkar, & R Core Team, 2016) package to fit the repeated-measures ANOVA and ‘multcomp’ (Hothorn, Bretz, & Westfall, 2008) package to conduct Tukey post-hoc tests.

Results

Individual-level behavior at cool and warm temperatures

In both temperature conditions, pups in all three age groups periodically appeared and disappeared from the huddle surface. The open circles in the two graphs in Figure 3a depict the activities of an 8-day-old focal pup on the huddle surface, showing that the frequency of appearances, and thus the total duration on the surface was greater in the warm condition.

In the cool environment, the average number of appearances/h was 31.75 (95% CI [21.88, 41.62]), 23.13 (95% CI [13.55, 32.70]), 19.00 (95% CI [9.08, 28.91]) for the P2, P4, and P8 groups, respectively (Figure 3b). In the warm condition, the average number of appearances/h was 21.50 (95% CI [13.98, 29.02]), 33.5 (95% CI [16.53, 50.47]), 54.88 (95% CI [35.92, 73.83]) for the same age groups, respectively. Thus, in the cool environment, there was an age-related decrease in the frequency of appearances on the huddle surface, whereas in the warm environment (36°C) the frequency of appearances on the surface of the huddle increased with age (Temperature $\times$ Age interaction effect: $F_{2, 11} = 9.55$, $p < .01$; Figure 3b). Pups show more positional changes in the warm environment than in a cool environment, which led to a main effect of Temperature ($F_{1, 33} = 6.59$, $p = .02$; Figure 3b). The main effect of Temperature was driven by the high levels of activity of the older pups in the warm environment; P8 pups were nearly three times more active in the warm nest than in the cool nest ($p = .046$, Tukey). In contrast, the posthoc tests of P4 and P2

pups between the two ambient temperatures were not statistically significant ($p = 1.0$, Tukey; for both comparisons). Because the activity of individual pups in the different temperature conditions was similar most of the time, Age was not a statistically significant predictor when tested as a main effect ($F_{2, 11} = 2.61$, $p = .12$).

Group-level behavior at cool and warm temperatures

The Styrofoam marker placed on the surface of the huddle at the beginning of each trial subsequently disappeared from view, but was visible most of the time when huddles were in a cool environment. This can be seen in the left panel of Figure 3a, which shows the percentage time the marker was obscured. The low values of time the marker was hidden indicates a downward “flow” of pup bodies, pushing and burrowing into the clump, leaving the marker floating on the huddle surface. Marker visibility averaged 7.13%, 28.84%, and 11.42% for the P2, 4, and 8 groups, respectively. We list here the 95% confidence intervals for each mean: $[-0.21, 14.48]$, $[-11.26, 70.94]$, and $[5.41, 17.43]$. When tested at 36° C, P2 and P4, focal pups were hidden for similarly modest percentages of time, 16.37% (95% CI $[-2.59, 35.33]$) and 19.64% (95% CI $[0.21, 39.07]$), respectively. Only the P8 pups in the Warm condition were visible most of the time. Thus, only P8 pups manifested regulated, directional flow. The temperature- and age-related differences in pup flow led to a statistically significant Temperature $\times$ Age interaction, $F_{2, 11} = 10.58$, $p < .01$ (Figure 3c). In a warm environment, the marker was hidden for more time than it was in the cool chamber leading to a main effect of Temperature ($F_{1, 31} = 9.99$, $p < .01$). This main effect was driven by the differences in marker exposure between P8 huddles tested in the warm and cool conditions ($p < .01$, Tukey). Posthoc comparisons between temperature conditions for P2 and P4 groups were not statistically significant ($p = 1.0$, Tukey; for both comparisons). In the Cool condition, the marker in the P8 huddles was hidden more than in the P2 huddles, which led to a main effect of Age ($F_{1, 11} = 7.37$, $p < .01$). The main effect was driven by differences between P8 and younger pups (P8-P4: $p < .01$, Tukey; P8-P2: $p < .01$, Tukey) as differences between P4 and P2 huddles were not statistically significant ($p = 1.0$, Tukey).

Discussion

Some implications of developmental findings

One striking result reported here is a developmental onset of regulated, directional pup flow by P8 mouse pups. During the first postnatal week, the pups' predominant intra-huddle movements were probing and diving downwards into the depths of the huddle, whether the ambient temperature was cool or warm. P8 huddles were the only age group to display temperature-dependent, directionally-regulated pup flow (downwards in the cool [22°C] and upwards in the warm [36°C] environments). This is not to say that pups (or huddles) less than 8-days of age are incapable of behavioral temperature regulation, but they do not respond to a warm challenge by reversing the direction of the pup flow. It is as if they are compelled to respond to the mélange of non-thermal cues in the huddle with the probing, pushing and diving that were their most frequent actions. By P8, however, their responses to the thermal challenge enable them to cease diving and instead, to move upwards, exposing more of their body surface to the surround, and enabling heat loss to the cooler surround.

It may be that altricial mammals are not well-prepared to combat warm challenges in early stages of life, when such thermal challenges are uncommon. A phenomenon of temperature-independent, persistent downward flow – even in warm nests – could allow pups to become hyperthermic and in that way alter their development. Such effects, then could result if global warming produces warmer nest environments. If altricial mammals are indeed vulnerable to hyperthermia, a consequence could be numerous possible cascading changes in physiology, behavior, and related cognitive developments (Figure 2).

Weaning in a Warmer World

Weaning refers to (a.) the phase in early life when offspring achieve independence from parental provisioning, (b.) the process of shifting to the consumption of solid food after relying on mother's milk, and (c.) a more general process of advancing toward independence from parental provisioning (Galef, 1981; Thiels & Alberts, 1991). A pivotal event in weaning (both as a phase and a process) is "leaving the nest". Rodents, like other altricial infants are born into a restricted and protective nest, where they receive parental attention and resources. To advance to the next major phase of their life, they must leave the nest and begin exposure to a myriad of new experiences and opportunities in the "outside world". Generally, the world outside the nest is more thermally variable, cooler, and challenging. Indeed, there is evidence that a pup's first egression from the nest and therefore the timing of many subsequent and formative milestones, depends on ambient temperature conditions outside the nest. In an earlier study from our laboratory (Gerrish & Alberts, 1996), individual rat dams and their litters residing in a "semi-natural" environment were observed on video from P14 – P22. The habitat consisted of a nestbox attached to a larger, open field in which powdered food was available. Ambient temperature of the field was either Warm (30°C), Moderate (21°C), or Cold (10°C); nest temperature was always Moderate. Behavior during 12 continuous hours was monitored and quantified from time-lapse video recordings. The pups' forays into the field and the onset of independent feeding were temperature-related: weaning was earliest in the warmth and increasingly late with decreased ambient temperatures. Among subjects in the Cold condition, there was a positive correlation between duration in the field and duration of feeding. Pups entering the Cold open field left the nest approximately long enough to feed, and then returned to the warm confines of the nest. In contrast, when pups in the Warm open field condition left the natal nest there was not a positive correlation between duration spent in the field and duration spent feeding. This was likely due to pups in warm environments showing additional behaviors outside the nest such as sleeping and playing.

To extend the idea that the thermally-fragile pre-weanling rat is freed by warmth and afforded the ability to foray from the confines of the insulative, natal nest, Gerrish, Onischak, and Alberts, 1998 employed a regime in which litters without their dam were exposed on P2 – P14 for 2 h/day to either a Cool, Moderate or Warm ambient temperature (10°C, 21°C, 31°C, respectively). Daily exposures to the Cold condition led to slower growth, delayed maturational markers such eye opening, and less insulative fur, relative to the pups in the Warm and Moderate conditions. Thermogenic capability, measured by oxygen consumption rate when challenged with an 18°C ambience did not differ across

groups. Time spent out of the nest and onset of independent feeding was a function of thermoregulatory development.

Ontogenetic Adaptations and Thermal Challenges

We have seen that in the young offspring of altricial species, such as mice and rats, thermoregulation is meager and poorly developed. Nevertheless, we have also learned that even the drastically-immature newborn can respond adaptively to thermal challenges with behavioral and physiological responses. Thermogenesis by the specialized organ of brown adipose tissue, combined with contact behavior is one such example (Cannon & Nedergaard, 2004).

An appraisal of the mammalian infants' repertoire of thermoregulatory responses yields a noteworthy pattern: Over all, the mammalian infant is better equipped with adaptive specializations for regulatory responses to cold challenges than for regulatory responses to heat challenges. Figure 1 provides a general picture of the overall pattern, as seen in the greater number of entries in the upper portion of the diagram, showing compensatory responses to cooling than in the lower portion where responses to warming are displayed. Of course, it is difficult to compare precisely the different types of mechanism with one another. Hoffman, Flory & Alberts (1999a) devised an operant head-turning procedure whereby 1-, 5- and 11-day-old rat pups in a cool environment could be rewarded with a 20-sec warming of the platform on which they lay. These investigators then established for each age "thermal preferenda" which was the pups' preferred surface temperature on a thermocline when the air temperature was either cool or warm. They then applied these air temperatures as the challenge in the operant setting; the surface preferenda established in the preliminary study were the precise rewards used in the learning task, thus equating the rewards according to the pups' preferences in the context of the two ambient temperatures. The results were dramatic. Whereas 1-, 5- and 11-day-olds learned the head-turning operant for the warm reward in a cool environment, only 5- and 11-day-olds acquired the head-turning response when rewarded with 20-sec cooling of the platform on which they lay. The 1-day-olds did not learn the task to combat heat challenge, although they learned the same operant for the equated reward of warming to the cold challenge (Hoffman, Flory & Alberts 1999b). It was clear in these studies that the 1-day-old pups were capable of using their behavior to serve body temperature homeostasis, for they regularly moved up the thermocline to very warm regions from which they retreated, and settled in areas that were adequately warm or cool to maintain a desirable temperature in a cool or warm environment, respectively (Eedy & Ogilvie, 1970; Hoffman, Flory, & Alberts, 1999a, 1999b).

The 1-day-olds' response patterns consisted of invariant and persistent orientation and turning to the warm stimulus or in its direction, which was likened to a "positive thermotaxis". This thermotaxis was so invariant that it prevented the newborns from learning a reversal of the original operant (Hoffman et al., 1999a). By 5-days of age, the pups' thermotaxis wanes sufficiently that they can respond actively to a cool stimulus and learn an association with it as a reinforcer.

Hoffman et al. (1999b) invoked the concepts of ontogenetic adaptation (Oppenheim, 1980) and developmental niche (Alberts & Cramer, 1988) to frame the newborns' initial lack of

learning to a cool stimulus and the subsequent expansion of their learning to include cool reinforcers. In the niche of the newborn, the key stimuli for survival, such as the mother's body, are warm. There are no obvious circumstances in which learning a novel response that could move a pup away from its mother and littermates would be beneficial. The initial existence of the strong, positive thermotaxis and absent reward value of cool stimuli, is consistent with an interpretation of ontogenetic adaptation.

Together with many of the phenomena reviewed earlier, as well as the original data on developmental differences in pup flow reported here, these considerations point toward recognition of the privileged roles of warm stimuli in the organization and establishment of early behavior in immature, altricial, endothermic species. Physiological and behavioral mechanisms, including learning, that serve to maintain thermal homeostasis in the face of cold challenges are the predominant, early-developing capabilities. Thus, thermotaxis, huddling, brown fat thermogenesis and the rewards of warming have developmental onsets prior to saliva spreading for evaporative cooling, pup flow in the upwards direction and cooling as a reinforcer.

These considerations underscore the utility of the concept of *ontogenetic adaptation*. This concept, especially as it was first elucidated by Oppenheim (1980, 1981) and further elaborated by others (e.g., Alberts & Cramer, 1988; Alberts & Harshaw, 2014; Galef, 1981; West & King, 2004) emphasizes that even at each early stage of ontogenesis, when development is obviously incomplete, that the developing organism can be a demonstrably complete and capable organisms at that stage – in relation to its typical, stage-related context. Thus, while a fetal rat is an inadequate infant, it nonetheless displays a host of features that enable it to survive and even flourish in a uterus; the newborn may be incapable of walking and foraging, but it is exquisitely formed and functional for locating and attaching to a nipple, suckling and utilizing mother's milk. Within the framework of ontogenetic adaptation, development is a series of adaptations to a sequence of habitats, each characteristic of a species' developmental environment. Natural selection acts on each stage of development, continuously shaping, refining and redefining the adaptations of development, relative to each ontogenetic niche as they are encountered (Gottlieb, 1987; Oyama, Griffiths, & Gray, 2003). Selection acts on the total, functioning organism at each stage (Laland et al., 2015). Thus, we see that behavior deserves a privileged position in ontogenetic adaptation (Gottlieb, 2002), which has more often focused on relatively isolated morphological or physiological characteristics.

The pattern we see in general, and in the data with altricial rodents in particular, suggests that infant mammals are ill-equipped to combat warm challenges, in comparison to their specializations of behavior and physiology for combating cold challenge. The mechanisms that are used by developing mammals for body temperature regulation integrate physiology and behavior (Gordon, 2012; Harshaw et al., 2017; Tattersall et al., 2012). In some cases, such as those involving huddling, group behavior, such as that of an aggregate of littermates is essential to effective thermoregulatory function. These stage-typical mechanisms are excellent candidates for consideration as ontogenetic adaptations.

Elevating Our Understanding of Developmental Responses to Thermal Challenges

We have discussed some of the ways in which mammalian development is shaped both directly and indirectly by thermal stimuli and environmental temperature. While it is true that infant mammals are buffered and protected from many perturbations, including thermal extremes, we have seen myriad pathways by which thermal conditions can affect developing organisms. We are struck, in particular, by the ways in which young mammals are ill-equipped to adapt to elevated temperatures, in comparison to cold temperatures. In addition, we can better see the limits of our knowledge and understanding of these basic processes, so this is also a call for a new generation of empirical questions, the answers to which might help us understand how infants adapt to elevated temperatures. Such thermal challenges that are likely to prevail with global warming and are clinically relevant to thermal-related pathologies.

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Fig. 1.

Snapshot view of responses of infant rodents to cool and warm ambient environments and their earliest reported developmental onset. The diagram depicts mostly mice in early postnatal development and rats in later postnatal life with other gaps filled with studies on sheep and hamsters. In each response box, the species from which the information is drawn is indicated in the upper left corner with the initial of the species—mouse (M), rat (R), hamster (H), and sheep (S). The pictures show the four major life history niches that are discussed in the paper: 1) The uterine environment, showing two fetuses in each uterine horn and their associated arterial blood vessels; 2) Mother-infant interactions, with the mother showing contact-dependent maternal care; 3) A group pups huddling; 4) A group of weanlings converging on a piece of food. References; Responses to cold: Prenatal (Cefalo & Hellegers, 1978; Laburn, Faurie, Goelst, & Mitchell, 2002; Schroder & Power, 1997); Thermotaxis (Leonard, 1974); BAT thermogenesis (Nedergaard, Connolly, & Cannon, 1986); Pup flow this study; Huddle contracts (Harshaw & Alberts, 2012); Shiver (Arjamaa & Lagerspetz, 1979); Piloerection (Pfister, 1990); Vasoconstriction (Conklin & Heggeness, 1971); Fur removal affects metabolism (Hahn, 1956); Insulative fat deposits (Hahn, 1956). Responses to warmth: Prenatal (Cefalo & Hellegers, 1978; Schroder & Power, 1997);

Huddle expands (Harshaw & Alberts, 2012); Pup flow (this study); Saliva spreading (Pfister, 1990).

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Fig. 2.

Known and predicted effects of elevated temperatures on maternal behavior and their consequences for infant development. Elevated temperatures are known to decrease maternal nest bouts, and lead to earlier weaning, increased play behavior and exploration in young. We speculate that elevated temperatures that decrease nest bouts will lead to decreases in contact-dependent maternal care such as maternal licking and grooming of the pups. Maternal care is known to have cascading effects on offspring cognition and behavior, such that pups with low-LG mothers are more aggressive during play, and have a lower reliance on social learning (Lindeyer, Meaney, & Reader, 2013), increased behavioral and physiological responses to stressors and anxiety (Caldji et al., 1998; Fish et al., 2004), decreased hippocampal synaptogenesis (Liu, Diorio, Day, Francis, & Meaney, 2000), and retardation in learning and memory (Champagne, 2008; Weaver et al., 2004). We suggests such changes in the cognition, behavior and physiology of offspring may occur in families, mothers and pups, exposed to warmer temperatures.

Fig. 3.

(a) Figurative and quantitative depiction of “pup flow” within a huddle of P8 mouse pups in a cool and warm nest. The graphs depict exposures of a marked, focal pup (grey open circles) and the styrofoam marker (black closed circles) on the surface of a huddle during sequential, 1 min intervals. The position of the black marker can be seen in relation to pups’ bodies—in a cool nest the marker floats, and in a warm nest the marker sinks. (b) The appearances of a focal pup at all ages in a cool and warm nest. The frequency of the response shows a clear linear developmental relationship in warm and cool nest, but in opposite directions. (c) Regulatory movement was confirmed only by P8 huddles, but not by younger groups. The predominant direction of the huddle was downward for P2, P4, and P8 huddles in a cool nest (22°C). In presence of a warm ambient air temperature (36°C), P8 huddles reversed direction and flowed upwards, whereas the direction of younger ages, P2 and P4, was continuously downward into the warm nest. The directional movements of the huddle as measured by the mean percentage of the time of the marker spent hidden during the one-hour experimental session. Error bars are one standard error.